



# WJMER

**World Journal of Medical Education and Research**

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**Students' Perception and Preference of Problem Based Learning at Moi University College of Health Sciences**

**Identification of the Potential Indications and Short-term Outcome of Intravitreal Injection of Bevacizumab at Regional Referred Eye Hospital in Madinah, Saudi Arabia**

**Does Clinical Training in Pediatrics Improve Med III Students Approach to Children? A Cohort Study**

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**Implementing Innovative Medical Education Strategy at Moi University College of Health Sciences: Are there Enough Resources?**

**Improving Medical Students Preparedness for Post-graduate Practice: A Supplementary Teaching Programme**

**A Case of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

**Rare Cases of Pneumatosis Intestinalis and Hepatic Portal Venous Gas without Bowel Ischaemia**

**A Study Evaluating the Awareness of International Medical Students About the Evolution and History of Medical Terminologies**

**First International Conference on RASopathies in Asia: Advances in RASopathies and Neurofibromatoses and in Identification of New Therapeutic Targets**

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## Introduction

The World Journal of Medical Education and Research (WJMER) (ISSN 2052-1715) is an online publication of the Doctors Academy Group of Educational Establishments. Published on a quarterly basis, the aim of the journal is to promote academia and research amongst members of the multi-disciplinary healthcare team including doctors, dentists, scientists, and students of these specialties from around the world. The principal objective of this journal is to encourage the aforementioned, from developing countries in particular, to publish their work. The journal intends to promote the healthy transfer of knowledge, opinions and expertise between those who have the benefit of cutting edge technology and those who need to innovate within their resource constraints. It is our hope that this will help to develop medical knowledge and to provide optimal clinical care in different settings. We envisage an incessant stream of information flowing along the channels that WJMER will create and that a surfeit of ideas will be gleaned from this process. We look forward to sharing these experiences with our readers in our editions. We are honoured to welcome you to WJMER.

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## WELCOME

We are delighted to bring you the fifteenth edition of the World Journal of Medical Education and Research (WJMER). This edition encompasses a variety of intellectually-stimulating articles, as well as the proceedings from the first International Conference on RASopathies in Asia which took place in Cochin, India between the 27<sup>th</sup> and 29<sup>th</sup> November 2017. The reader of this edition of the WJMER will be offered an insight into the innovative and encouraging research that is currently being conducted throughout the world.

The opening article by Katwa *et al.* examines the way in which students at Moi University College of Health Sciences, Kenya evaluate the SPICES model, a paradigm that can be implemented in the planning and development of a curriculum and in the consolidation of certain teaching methods and modes of assessment. This study specifically considers students' perceptions of problem-based learning versus lecture-based learning.

Alahmadi *et al.* highlight the indications of the bevacizumab intravitreal injection, as well as assess the short-term outcomes of the procedure. The study uses a cohort of patients who have received the injection at a local eye hospital in the Madinah region of Saudi Arabia.

Recognising the complexity of performing a clinical examination on a child patient, Joey *et al.* explore the value of an additional training programme aimed at medical students that is centred on developing a suitable clinical approach to paediatric patients.

Singh *et al.* undertake a qualitative study in order to assess the effectiveness of the Royal College of Surgeons of Edinburgh 'Future Surgeons: Key Skills Course' on its attendees, namely medical students and Foundation Year Doctors. It uses a pre-course and post-course questionnaire which asks delegates to rate their confidence in the various surgical skills that were taught during the course. The results are analysed and the educational effectiveness of the course is evaluated.

The following article by Katwa discusses the role of the innovative medical education strategy. The success of this strategy in resource-poor settings is questioned, and the availability of sufficient resources to allow it to be successfully implemented in these countries is explored. This study specifically focuses on Moi University College of Health Sciences, Kenya.

Nurse and Jones intend to improve the confidence of medical students who are in their final year of study and preparing to enter the role of a Foundation Year Doctor. In an attempt to assist these aspiring medics in their transition from students to junior doctors, the authors create and implement a teaching programme which features a series of lectures, simulation tasks, and small-group teaching sessions.

Vamsi *et al.* attempt to determine the development of multi-drug resistant tuberculosis in patients with depression. In the penultimate article, Lim *et al.* examines rare cases of pneumatosis intestinalis and of the presence of hepatic portal venous gas which are not associated with bowel ischaemia.

In the final article, Williams and Enoch report a study that evaluated the awareness of International Medical Students about the evolution and history of medical terminologies. They surmise that medical students have a limited understanding of the Greek or Latin origin of medical terminologies and that, as a result, their ability to comprehend the meaning of certain medical terminologies might be hindered.

The proceedings from the first International Conference on RASopathies in Asia follow the aforementioned articles. These illustrate the ground-breaking research that is currently being conducted within this field throughout the world.

We sincerely hope that you find each article in this edition enlightening, thought-provoking and enjoyable to read.

With very best wishes,

**Ms Karen Au-Yeung**  
Editor

**Ms Rebecca Williams**  
Associate Editor

**Professor Stuart Enoch**  
Editor-in-Chief

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## Students' Perception and Preference of Problem Based Learning at Moi University College of Health Sciences

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### Abstract

**Introduction:** The purpose of this study was to assess the perception and preference of the SPICES model among students at the Moi University College of Health Sciences. We can define innovative teaching and learning method or the SPICES model as a program or series of events which the teacher implements to assist the student to remain focused on what that individual is doing. Problem-based learning is considered superior to the lecture-based learning due to long-term retention of knowledge, development of generic skill and attitudes. This study looked into the students' views of problem-based learning versus lecture-based learning in Moi University College of Health Sciences.

**Methods:** 274 students were divided to School of Medicine, School of Public Health, School of Nursing and School of Dentistry as per their number of students in each school. Self-administered questionnaires were used in quantitative data collection while in-depth interviews quantitative were used in qualitative data collection. A reliable and valid questionnaire utilized a five-point forced Likert scale (1-Totally disagree, 2-Disagree, 3-Not Sure, 4-Agree, and 5-Totally Agree). Cronbach's alpha, median and inter-quartile range (IQR) were calculated in SPSS 22. P-value less than or equal to 0.05 was taken as statistically significant. Ethical approval was obtained from the Institutional Review and Ethics Committee (IREC) of Moi University and Moi Teaching and Referral Hospital.

**Results:** The response rate among students was 250 (91%) out of 274 who were given questionnaires. Majority of the students 179 (72 %) preferred SPICES model compared to 71 (28 %) who preferred lecture method of learning. A chi-square test to determine the measure of association between schools and preference of Problem Based Learning and Lecture method of learning showed no statistical significance with a P-value of 0.092; at  $p < 0.05$ .

**Conclusions:** Problem based learning is fun, provides contextual learning and imparts long-term retention of knowledge through students' active participation in a small group. It also promotes generic skills and self-directed life-long learning.

### Key Words

Medical School; Perception; Problem Based Learning; Students; Lecture

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**Introduction:** The purpose of this study was to assess the perception and preference of the SPICES model among students at the Moi University college of Health Sciences. We can define innovative teaching and learning method or the SPICES model as a program or series of events which the teacher implements to assist the student to remain focused on what that individual is doing. It stimulates the students' ability to engage in problem-solving activities that make a student an expert in his/her area of concentration. This process makes a student an active learner and the teacher a facilitator as opined<sup>1</sup>.

Innovative approach to learning was facilitated by the growth of technology in 19<sup>th</sup> century<sup>2</sup> argues

that the introduction of instructional media in teaching facilitated various innovative opportunities. To meet the needs of innovative teaching and learning method, majority of the institutions who adopted it opted for problem-based teaching and learning method. Flavio argues that problem-based teaching and learning method is becoming increasingly popular in educational institutions because of actively being able to engage students in constructing knowledge<sup>3</sup>. Innovative method of teaching and learning adopted by medical colleges then is the problem-based learning. Koh *et al* opines that problem-based learning have been introduced to improve the quality of graduating health professionals. They argue that graduates taught using problem-based learning method are more

competent and systematic compared to the ones trained using traditional lecture method<sup>4</sup>.

Problem-Based Learning (PBL) is a teaching method in which complex real-world problems are used as the vehicle to promote student learning of concepts and principles as opposed to direct presentation of facts and concepts. In addition to course content, PBL can promote the development of critical thinking skills, problem-solving abilities, and communication skills. It can also provide opportunities for working in groups, finding and evaluating research materials, and life-long learning<sup>5</sup>

**Methods:** This research is a descriptive cross-sectional study design which utilizes both qualitative and quantitative method of data collection. The goal of mixed methods is not to replace either of these approaches but rather to draw from the strengths and minimize the weaknesses of both methods. Data was collected from September to December 2016. From the 1,200 student population; first year students were excluded for being new to the program. Their views might not reflect the actual scenario on the ground. This brings the target population of students to 940; distributed as follows: - School of Medicine 570 (61%), Public Health 160 (17%), Nursing 130 (14%), and Dentistry 80 (8%). All students in year two of their studies and above had equal chance to participate they were all currently using the SPICES model as a way of learning and comparing it with the lecture method which was used in high school. Probabilistic and non-probabilistic techniques were used in recruiting research participants. The sample size of 274 for students is the representative of all the four schools; to distribute the figure of 274 to four schools; stratified sampling was used. In a stratified procedure, 274 sample sizes were divided to School of Medicine, School of Public Health, School of Nursing and School of Dentistry as per their number of students in each school; resulting to 166: 47: 38: 23 respectively. Self-administered questionnaires were used in data collection; the questionnaire was designed with the intention of answering the research questions and objectives. This questionnaire utilized a five point forced Likert scale (1-Totally disagree, 2-Disagree, 3-Not Sure 4-Agree and 5-Totally Agree), test-retest and Cronbach's alpha test were used to test the validity and reliability of the questionnaire. The questionnaire also consisted of an open-ended section to comment on the PBL process contents; thematic analysis was used to analyze data collected from this section. Data entry was done in SPSS version 22. Descriptive statistics were presented using median and interquartile range. Cronbach's alpha was used to test the validity and reliability of

the questionnaire. P-value less than or equal to 0.05 was taken as statistically significant. Ethical approval was obtained from the Institutional Review and Ethics Committee (IREC) of Moi University and Moi Teaching and Referral Hospital.

**Results:** The response rate among students was 250 (91%) out of 274 who were given questionnaires. Student participants who returned the questionnaires were drawn from the four schools in the College of Health Sciences; the highest numbers of students were from the School of Medicine 145 (58 %) with the lowest from the School of Dentistry 21 (8 %). The tool was highly reliable with internal construct reliability more than 70% (Cronbach's alpha = 0.77). Majority of the students 179 (72 %) preferred SPICES model compared to 71 (28 %) who preferred lecture method of learning. Forty eight (68 %) who preferred lecture method of learning were from the School of Medicine, 11 (16 %) from School of Public Health, while 5 (7%) were from the School of Nursing, 7 (10 %) were from School of Dentistry. A chi square test to determine the measure of association between schools and preference of Problem Based Learning and Lecture method of learning showed no statistical significance with a P-value of 0.092; at  $p < 0.05$ .

Students also expressed different views during qualitative interviews on how to improve the SPICES model. One student felt that a repeat of training first year students in PBL method of teaching and learning should be done during the second term of 1<sup>st</sup> year. Students will have identified the problematic areas of this mode of teaching and learning he said:

*"Orient students in PBL method of teaching and learning during first one week in second term of first year".*

Other students felt like the University need to add more equipment's they said:

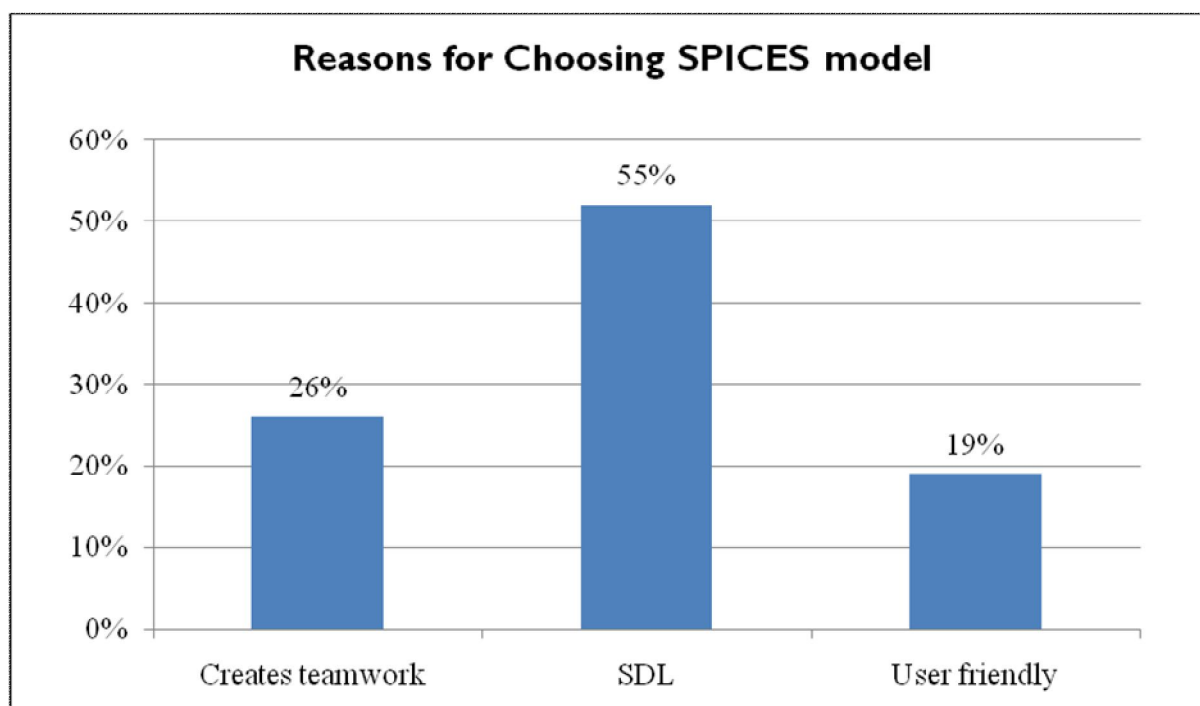
*"Equip library, subscribe e-books and avail internet" while the other one said "Equip the library, ensure that there is wireless internet in all lecture halls and tutorial rooms".*

Another approach the study found of ending this confusion is by improving lecturer student relationship. Student participant 141 stated:

*"Improve student lecturer relationship."* Another student participant 220 stated

*"Provide mentorship for younger students to motivate them".*

If there is good relationship between lecturers and students, lecturers as mentors will be able to influence the new students to know the areas they are required to concentrate in their studies hence improving the outcomes of the SPICES model.



**Figure 1 :** Reasons for Choosing SPICES Model by Students

#### Perception and preference scores for SPICES model

Out of the students who preferred SPICES model; 98 (55 %) preferred this method of learning because it is self-directed which gives them adequate time to prepare and also read at their own phase. A group of 46 (26%) prefer SPICES model because it creates a spirit of teamwork, and another 34 (19%) preferred SPICES model because they find it to be flexible and user friendly as per *Figure 1*.

As indicated in *Table 1* below students in year four of their studies, given an option to choose between

SPICES model versus lecture method of teaching and learning 53 (78 %) would choose SPICES model. The School that is having the highest percentage of students opting for SPICES model was the School of Nursing with 32 (84%). School of Dentistry has the highest percentage of students who would opt for lecture method of teaching and learning at 7 (30%); followed by School of Medicine with 48 (29%). Generally in all the four schools, more than 50% of their students would opt for SPICES model of teaching and learning, it ranges from 58% being School of Medicine to 84% being School of Nursing.

Learning Method	Year of Study					
	2	3	4	5	6	Total
High School (Lecture)	16	17	15	15	8	71
SPICES model	45	44	51	19	29	179
Total	61	61	66	34	28	250

**Table 1:** Comparing SPICES Model to Lecture Method of Teaching among Classes

Ser.	Responses	Percentage
	<b>Students</b>	
1	It is confusing rarely do we know what is expected from us	23%
2	Demands a lot from the student	29%
3	Creates excuse for lecturers absenteeism that students are doing SDL	23%
4	Overcrowded tutorial groups	25%

*Table 2: Challenges of SPICES model as viewed by students*

### Challenges faced by students concerning SPICES model

Students were asked to name the weaknesses of SPICES model; 58 (23%) of them said that the program is confusing; rarely do we know what is expected of us. Others, 72 (29%) said it demands a lot from the student; while 58 (23%) hold the view that this system gives excuse to the lazy lecturers to avoid going to class to teach in the name of the students doing self-directed learning. Sixty two students (25%) think that tutorials are overcrowded, as per Table 2.

### Discussion

None of the students in all the four Schools had gone through the SPICES model in their high school education. All of them said they first encountered SPICES model upon reporting to the College of Health Sciences. However, when asked to state the program they would opt for, given a chance to choose between Lecture method of teaching and SPICES model, majority in all the four Schools said they would prefer SPICES model. They gave three reasons for their likely choice, namely: that it is user-friendly; creates teamwork spirit among the students, and that it enables a student do his/her self-directed learning at own phase. Indeed, SPICES model is student-centered because the student is the one leading the learning session; the lecturer merely becomes a facilitator. The findings agree with the view that SPICES model is a student-centered approach<sup>1</sup>.

A cross-tabulation of student participants and their schools was done to determine if there was any relationship between being a member of a particular school and the level of preference of SPICES model method of teaching and learning. A Chi-square test was carried out which established no statically significant association between their school and the choice of SPICES model over lecture method in the schools of SOM, SPH and SON. This meant that every student had equal chance of understanding SPICES model of teaching and learning in the College of Health Science regardless of their alma mater. This finding agrees with the views of another study done by Majumder<sup>6</sup>.

SPICES model of teaching and learning recognizes the principles of adult learning, which give autonomy to every student to study the way they know best. The principles of adult learning give credit to learners; which enables them to join a new program with past experience and setting priorities on what they want to know, a view supported by both<sup>7, 8</sup>.

The findings on students' awareness in all the four Schools on SPICES model elicited many views. Most of them understood SPICES model as a student-centered learning process. In agreement, others simply explained SPICES model as a move-away from the lecture method in which the central person is the student. Indeed, in SPICES model, the central person is the student and the lecturer is merely a facilitator. The lecturer acts as a resource person but students are the ones seeking solutions to the set problems. SPICES model leads learners to learn by discovery. It shifts the responsibility of learning from the teacher to the learner. Students become active participants, involved as much as possible in all activities and they own the solutions they<sup>9</sup>.

Though students would opt for SPICES model, given to choose between SPICES model and lecture method, lecturers if given the option to choose, majority would opt for mixed method. This shows that the induction students go through during orientation has had an impact in understanding SPICES model of teaching and learning to them, but it has not caused impact to lecturers. Among the lecturers, induction and other issues; such as lack of teaching materials still hinder them from preferring SPICES model of teaching an observation that agrees with that of Hudson in a study done in 2015<sup>10</sup>.

Majority of the students in all the Schools admitted that self-directed learning motivated them in college and would benefit them after graduation. This view has been supported by<sup>11</sup>. Other benefit of self-directed learning includes the fact that the amount of time students spend on a particular subject is left to them and the responsibility of retaining what they have learned for future use<sup>12</sup>.



The study further established that teamwork among students in all the four Schools has been facilitated through electives and community-based education and service (COBES). Majority of the student participants said that COBES and electives had helped them to improve in their academic performance. They said that the COBES programs had enhanced their performance because students were integrated from four schools enabling them to learn from one another. When health professional trainees put their expertise together, they are able to tackle difficult health problems from all dimensions<sup>13, 14</sup>.

The other benefit of electives and COBES is that they provide an opportunity for medical students to encounter real health problems of the community. During COBES and electives; students were challenged to provide solutions to existing community's health problems. This provided an alternative, practical and realistic approach to learning and problem-solving<sup>14</sup>.

The students were also faced with challenges in the SPICES model as some lecturers were absenting themselves from class. These lecturers absented themselves arguing that students were engaged in self-directed learning and therefore did not need the instructor. In Makerere University, for example, it was noted that some lecturers who did not understand SPICES model of teaching avoided taking part in some courses a view also observed by both<sup>15and16</sup>. To overcome this problem, it was recommended that there was a need to ensure that lecturers attended classes through improved supervision of program; and workshops on SPICES model of teaching and learning. This will equip the lecturers with skills and courage to enable them attend class<sup>10</sup>.

Some students complained that they did not understand SPICES model during orientation. Some of them observed that the previous lecture method did not prepare them for change<sup>17</sup>. Some of the students said the SPICES model was confusing, especially in regard to the much that is expected of them by the instructors. Others still complained that SPICES model demanded too much from them. These findings indicate the need to repeat SPICES model training later following the one done when first years were being orientated. Students suggested that SPICES model training be repeated during second term in first year when they will have identified the challenges in it. Students must be fully prepared on how to use SPICES model to avoid confusion over what is expected of them as observed by both<sup>18and17</sup>. Even though SPICES model is a student-centered approach to training, learners still need constant interaction with the lecturers. As

mentors, lecturers can help new students to identify the areas they need to pay closer attention to in their self-directed studies as agreed by<sup>16</sup>. Therefore, regular interaction between students and lecturers can reduce the problem of students finding SPICES model too overwhelming. Lecturers can help students adjust to SPICES model of teaching and learning<sup>17</sup>.

### Conclusions

That majority of students led by fourth years across all schools would opt for SPICES model of teaching and learning, given the option of choosing the method of teaching and learning between SPICES model and lecture method. Students applied the principles of innovative teaching and learning in their studies. Supervision of lecturers, students and administrators should be intensified by having monthly administrative meetings to receive progress reports on the challenges of teaching and learning and hence solutions would be agreed upon.

### Competing interests

The authors declare that they have no competing interests.

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## Identification of the Potential Indications and Short-Term Outcome of Intravitreal Injection of Bevacizumab at Regional Referred Eye Hospital in Madinah, Saudi Arabia

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### Abstract

**Background:** Bevacizumab is a monoclonal antibody that binds to all kinds of vascular endothelial growth factor (VEGF) and is successfully used as a systemic drug in treatment of cancers<sup>1</sup>. Several previous studies have revealed the usefulness of the intravitreal injection of bevacizumab in treatment neovascularization and macular edema secondary to several eye diseases<sup>2-11</sup>.

**Purpose:** To point out the indications and assess short-term outcome of bevacizumab intravitreal injection at Regional Referred Eye Hospital in Madinah Area, Saudi Arabia.

**Methods:** The study included 59 eyes of the studied patients submitted to intravitreal injection of bevacizumab at Regional Referred Eye Hospital in Madinah Area, Saudi Arabia, during the period from June to December 2015. At baseline, visual acuity and optical coherence tomography (OCT) were measured and data sheet was filled for each studied patient. The outcome variables in terms OCT thickness in micrometers and visual acuity were measured three months after injection. The data were analyzed by appropriate statistical tests.

**Results:** Of the 59 studied eyes, the majority 35 (59.3%) were diagnosed as diabetic macular edema (DME), 9 (15.3%) as proliferative diabetic retinopathy (PDR), 5 (8.5%) as combined PDR and vitreous hemorrhage (VH), 4 (6.8%) as combined DME and PDR, 2 (3.4%) as choroidal neovascularization (CNV) secondary to age-related macular degeneration, 2 (3.4%) as macular edema secondary to central retinal vein occlusion (CRVO), 1 (1.7%) as macular edema secondary to branch retinal vein occlusion (BRVO) and 1 (1.7%) as neovascular glaucoma. Compared to baseline mean OCT thickness, there was a statistically significant decrease in mean OCT thickness measured three months after injection. It was markedly decreased in patients aged  $\leq 60$  years (54.2%), male patients (37.2%), type II diabetics (52.5%), best corrected visual acuity of  $\geq 0.1$  (45.7%), non-hypertensive (42.3%), and those with DME (38.9%), with PDR (8.4%), with PDR and VH (8.4%) and those with DME and PDR (6.7%) more than 10%. Moreover, the visual acuity was improved in 9 (43%) out of 21 eyes with baseline visual acuity  $< 0.1$  Decimal.

**Conclusions:** Diabetic macular edema was the commonest indication followed by proliferative diabetic retinopathy. In addition, the study confirms the accumulating evidence of the usefulness and short-term efficacy of intravitreal injection of bevacizumab. The study suggests the need for further investigations with larger multicenter randomized studies in our region and a longer follow up to verify if this improvement is sustainable or not. However, the major concern is the need for increasing awareness about the importance of diabetes control and its impact in our region.

### Key Words

Intravitreal; Macular Edema; Bevacizumab; Diabetes Mellitus; Saudi Arabia

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### Introduction

Bevacizumab is a monoclonal antibody that binds to all kinds of vascular endothelial growth factor (VEGF) and is successfully used as a systemic drug in the treatment of cancers<sup>1</sup>. VEGF is known to have a pivotal role in the process of neovascularization and increasing vascular permeability in diabetic eyes<sup>2</sup>. Apart from laser photocoagulation, which is the primary treatment modality, intravitreal injection of

bevacizumab was used widely in treatment of various types of macular edema. Several previous studies have revealed the usefulness of the procedure in decreasing macular edema secondary to central retinal vein occlusion, fibrovascular proliferation secondary to proliferative diabetic retinopathy (PDR), and choroidal neovascularization (CNV) secondary to age-related macular

degeneration and secondary to vogt-koyanagi-harada syndrome (VKH)<sup>3-12</sup>.

In animal studies, no toxicity was noted following intravitreal bevacizumab injection in albino rabbit retina at different concentrations up to 2.5 mg<sup>13</sup>. In human studies, however, some rare systemic and ocular complications have been reported. The systemic complication included increase in blood pressure, followed by cerebrovascular accidents and myocardial infarction<sup>14</sup>. Endophthalmitis, a severe ocular complication, was also reported in previous studies<sup>15</sup>. The prognostic value of patients' characteristics such as age, gender, and best-corrected visual acuity (BCVA) at baseline were analyzed in other studies<sup>16-18</sup>. These studies identified young age, male gender, and good BCVA at baseline as favorable prognostic factors.

Although the wide indications of use of intravitreal bevacizumab injections, in the Saudi literature there was no overall collective indications of the usefulness of this intravitreal drug for variety indications. From this point of view, the present study aimed to point out the collective and frequent indications of intravitreal bevacizumab and assessing the short-term outcome of patients treated with intravitreal Bevacizumab injections at the regional referred eye Hospital in Madinah Area, Saudi Arabia.

### Methods

The present follow up study included 59 eyes of the studied patients submitted to intravitreal injection of bevacizumab at regional referred Eye Center of Ohoud Hospital in Madinah Area, Saudi Arabia during the period from June to December 2015. All patients who met the inclusion criteria at Eye Center of Ohud Hospital of both genders came for their first intravitreal bevacizumab injection and aged more than 18 years were eligible for the study. The exclusion criteria included, patients having bleeding disorder, active ocular infection, previous history of intravitreal bevacizumab, recent myocardial infarction, pregnancy and previous history of laser photocoagulation.

The visual acuity and optical coherence tomography (OCT) were measured and data sheet was filled at the baseline (one week before bevacizumab injection). OCT was done on Topcon 3D OCT 2000 (picture angle 45 degrees with an in-depth resolution of 5 micrometer) prior to procedure using the Cirrus HD-OCT device to assess the macular thickness. Intravitreal injection of 1.25 mg/0.05ml of bevacizumab was injected 3.5-4mm from limbus under local anesthesia by the Doctor in charge. Post procedure OCT was done on all

studied patients three months after injection and the final outcome was determined on the basis of macular thickness in micrometers. Visual acuity was also measured.

DME was defined as retinal edema or hard exudates within 500micrometers of the center of macula, retinal edema one disc diameter or larger, any part of which was within one disc diameter of center of macula as evaluated on OCT<sup>20</sup>.

All data analyses were done using statistical analysis system (SAS) software package<sup>19</sup>. The data were presented as mean  $\pm$  SD for continuous variables and frequencies and percentages for categorical variables. The mean OCT diameters were compared before and after bevacizumab injections using paired *t* test. In order to compare the the percent reduction in the thickness of OCT, three months following injection of bevacizumab, among the studied patients, chi square, Fischer exact and McNemar tests were used as appropriate. P value  $\leq$  0.05 was considered as an indicator of statistically significant difference. Ethical consideration was taken to ensure the confidentiality and privacy of the collected data. Written consent was taken from all studied patients. Patients who were mentally not able to give consent and those refused to participate were excluded from the study. Deanship of Scientific Research Ethics Committee at Taibah University, Madinah, Saudi Arabia, approved the study protocol.

### Results

The study analyzed data from 59 eyes of the studied patients. The mean age of the patients was  $56.7 \pm 10.9$  years, of them 78% were  $\leq 60$  years old. More than one half of them (55.9%) were male. The majority of the studied patients (79.7%) were type II diabetic patients. Less than half of patients were hypertensive (39%). Of the studied subjects the majority, 35eyes (59.3%) were diagnosed as diabetic macular edema (DME), 9 eyes (15.3%) as proliferative diabetic retinopathy (PDR), 5 eyes (8.5%) as combined PDR and vitreous hemorrhage (VH), 4 eyes (6.8%) as combined DME and PDR, 2 eyes (3.4%) as choroidal neovascularization (CNV) secondary to age-related macular degeneration (ARMD), 2 eyes (3.4%) as macular edema secondary to central retinal vein occlusion (CRVO), 1 eye (1.7%) as macular edema secondary to branch retinal vein occlusion (BRVO) and 1 eye (1.7%) as neovascular glaucoma. The mean OCT macular thickness for all studied patients at their baseline was  $425.2 \pm 168.9$  micrometers. Also, the baseline of best corrected visual acuity ( $\geq 0.1$  Decimal) was found in 64.4% of the studied patients (Table 1).



Characteristics*	N= 59
<b>Age in years</b> , mean $\pm$ SD (Range)	56.7 $\pm$ 10.9 (24-80)
<b>Age in categories</b> $\leq$ 60 years > 60 years	46 (78.0) 13 (22.0)
<b>Patients' sex</b> Male Female	33 (55.9) 26 (44.1)
<b>Diabetes mellitus</b> No Type I Type II	4 (6.8) 8 (13.5) 47 (79.7)
<b>Hypertension</b> No Hypertension	36 (61.0) 23 (39.0)
<b>Eye diseases</b> DME PDR PDR + VH DME + PDR CNV Macular edema secondary to CRVO Macular edema secondary to BRVO NV glaucoma	35 (59.3) 9 (15.3) 5 (8.5) 4 (6.8) 2 (3.4) 2 (3.4) 1 (1.7) 1 (1.7)
<b>OCT in micrometers before injection</b> , mean $\pm$ SD (Range)	425.2 $\pm$ 168.9 (137-862)
<b>Visual acuity on presentation</b> $\geq$ 0.1 < 0.1	38 (64.4) 21 (35.6)

\*Data are presented by mean  $\pm$  SD or by n (%).

**Table 1:** Characteristics of Studied Patients

Patients' characteristics	Before injection	After 3 months	P value
<b>All studied patients (n=59)</b>	425.2 ± 168.9	370.5 ± 143.7	0.04*
<b>Age categories</b> <60 years ≥ 60 years	421.7 ± 156.5 468.2 ± 108.6	349.5 ± 162.7 435.2 ± 117.7	0.03* 0.20
<b>Patients' sex</b> Male Female	422.3 ± 164.5 441.7 ± 181.7	337.7 ± 122.6 369 ± 152.9	0.01* 0.19
<b>Diabetes mellitus</b> No Type I Type II	668.3 ± 148.7 443.6 ± 188.9 410.6 ± 159.1	515. ± 133.1 304.4 ± 205.7 385.1 ± 148.3	0.43 0.14 0.28
<b>Hypertension</b> No Hypertension	407.3 ± 150.2 465.5 ± 201.3	368.1 ± 157.2 410.8 ± 158.5	0.21 0.25
<b>Reasons</b> DME PDR PDR + VH DME + PDR CNV Macular edema CRVO Macular edema BRVO NV glaucoma	421.8 ± 154.2 507 ± 181.4 96.0 ± 214.6 381.7 ± 180.8 624.5 ± 47.3 453.9 ± 186.3 668.3 ± 148.7 513.2 ± 85.2	317.3 ± 116.3 459.5 ± 163.4 337.8 ± 197.3 203.2 ± 37.1 559.5 ± 48.7 369.5 ± 177.2 515.6 ± 133.1 465.2 ± 80.5	0.01* 0.15 0.28 0.08 0.95 0.04* 0.03* 0.04*
<b>Visual acuity</b> ≥ 0.1 < 0.1	400.9 ± 152.1 500.4 ± 195.7	358.9 ± 152.0 446.1 ± 154.6	0.04*

\*Significant

**Table 2:** Comparison of Mean OCT Thickness before and after Bevacizumab Injection by Patients' Characteristics: Three Months Follow Up.

Table 2 compared the mean OCT thickness of the studied patients before and after Bevacizumab injection by their characteristics. Statistically significant difference was detected between the mean OCT thickness before and after injection among all studied patients ( $p=0.04$ ). Also, a significant reduction in the mean OCT thickness after Bevacizumab injection was observed among patients less than 60 years ( $P=0.03$ ), and male patients ( $p=0.01$ ). Examining patients by the reason of Bevacizumab injection, the

mean OCT thickness was decreased after Bevacizumab injection for studied reasons and did show statistically significant differences among patients presented with DME, Neovascular glaucoma, Macular edema secondary to BRVO, and among those patients presented with Macular edema secondary to CRVO. Patients with best corrected visual acuity of  $\geq 0.1$  Decimal, showed significant decrease in the macular thickness after injection ( $p=0.04$ ).

Patients' characteristics	> 10 % n (%)	≤ 10 % n (%)	P value
<b>All studied patients (n=59)</b>	41 (69.4)	18 (30.5)	-
<b>Age categories</b> ≤60 years > 60 years	32 (54.2) 9 (15.2)	14 (23.7) 4 (6.7)	0.98
<b>Patients' sex</b> Male Female	22 (37.2) 19 (32.2)	11 (18.6) 7 (11.8)	0.59
<b>Diabetes mellitus</b> No Type I Type II	3 (5.0) 7 (11.8) 31 (52.5)	1 (1.6) 1 (1.6) 16 (27.1)	0.45
<b>Hypertension</b> No hypertension	25 (42.3) 16 (27.1)	11 (18.6) 7 (11.8)	0.99
<b>Reason</b> DME PDR PDR + VH DME + PDR CNV Macular edema secondary to CRVO Macular edema secondary to BRVO NV glaucoma	23 (38.9) 5 (8.4) 5 (8.4) 4 (6.7) 1 (1.6) 2 (3.3) 1 (1.6) 1 (1.6)	12 (20.3) 4 (6.7) 0 (0.0) 0 (0.0) 1 (1.6) 0 (0.0) 0 (0.0) 0 (0.0)	0.25
<b>Visual acuity</b> ≥ 0.1 < 0.1	27 (45.7) 14 (23.7)	11 (18.6) 7 (11.8)	0.72

**Table 3:** Reduction in OCT Thickness after Bevacizumab Injection by Patients' Characteristics: Three Months Follow Up

Table 3 presented the percent reduction in the macular thickness of OCT following injection of bevacizumab at three months follow up. Macular thickness after three months of injection was decreased. In the eyes of the studied patients with decreased macular thickness, there were 41 eyes (69.4%) with ≥10% decrease in macular thickness, 18 eyes (30.5%) with < 10% decrease in macular thickness.

Although, there were no statistically significant dif-

ferences in the percent reduction, the higher proportion of eyes with > 10% macular thickness reduction was among patients aged ≤ 60 years (54.2%), male patients (37.2%), type II diabetics (52.5), best corrected visual acuity of ≥ 0.1 (45.7%), non-hypertensive (42.3%), and those with DME (38.9%). The patient presented with neovascular glaucoma in this study showed more than 10% reduction in macular thickness after Bevacizumab injection.

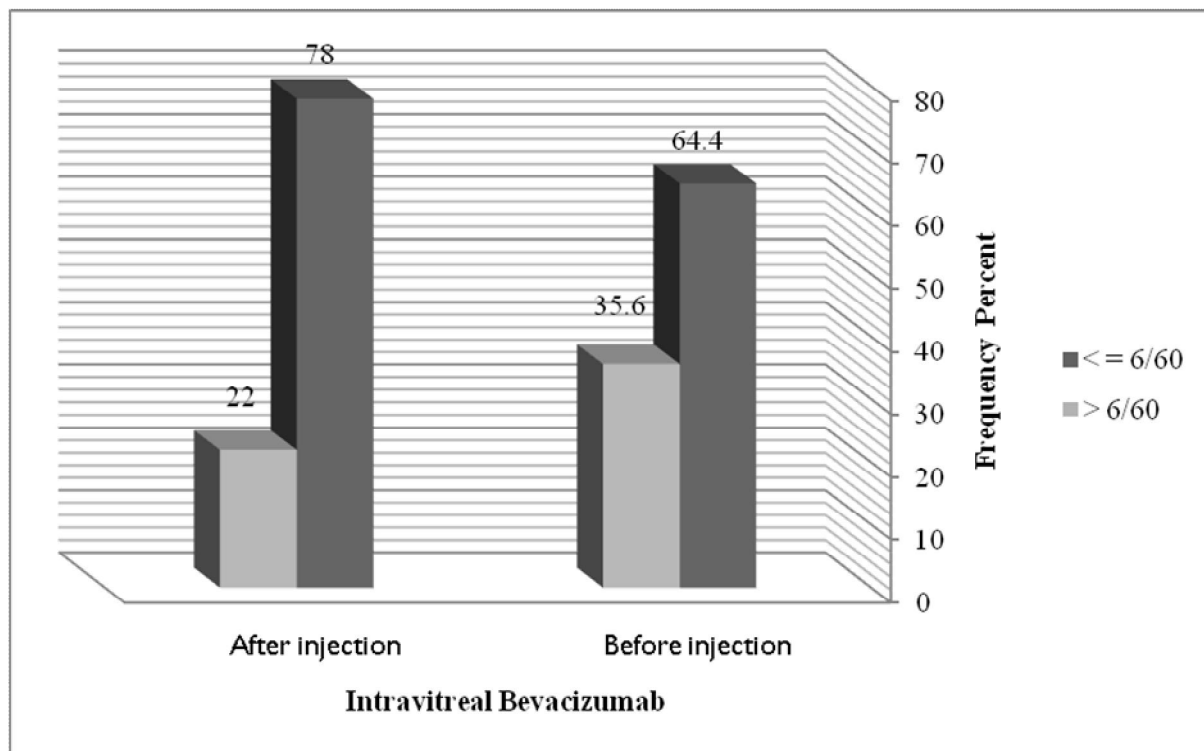


Figure 1: Comparison of Visual Acuity before and after Bevacizumab Injection: Three Months Follow up.

Visual acuity	Before injection n (%)	After injection n (%)	P value
≥ 0.1	38 (64.4)	46 (78.0)	0.01*
< 0.1	21 (35.6)	13 (22.0)	
Total	59	59	

Table 4: Comparison of Visual Acuity before and after Bevacizumab Injection: Three Months Follow Up

\*Significant

Figure 1, Table 4 showed comparison of patients' visual acuity before and after bevacizumab injection. Out of the studied 59 eyes of the studied patients, there were 38 eyes (64.4) with best corrected visual acuity of  $\geq 0.1$  Decimal at baseline. After injection, the frequency of eyes with best corrected visual acuity was significantly increased ( $p=0.01$ ) to reach 46 eyes (78%). Paired analyses of the above mentioned figured was revealed that 9 (43%) out of studied 21 eyes with baseline visual acuity  $<0.1$  were improved. Meanwhile only one eye (7.7%) of the studied 38 eyes with baseline visual acuity  $\geq 0.1$  was deteriorated.

#### Discussion

The present case series follow up study included 59 eyes of the studied patients attending Ohoud

Hospital, Madinah, Saudi Arabia; 35 eyes were diagnosed with DME, 9 with PDR, 5 with PDR and VH, 4 with DME and PDR, 2 with CNV secondary to ARMD, 2 with Macular edema secondary to CRVO, 1 with Macular edema secondary to BRVO and 1 with neovascular glaucoma. All cases were submitted to intravitreal injection of bevacizumab at eye center of Ohoud hospital, Madinah, Saudi Arabia during six-months study period from June to December 2015. Neither systemic nor ocular complications were seen in all studied patients during the study period. Absence of complications in this study was also noted in similar previous studies<sup>20,21</sup>. On the other hand, a large uncontrolled clinical study included 4303 patients has reported cardiovascular and cerebrovascular complications in 18 patients, and bacterial endophthmlitis in 7



patients<sup>15</sup>. In that study, however, the used inclusion and exclusion criteria were not so coherent that the potential risk of complications would not be prevented. In our and other similar studies, however, many patients with suggested risk of developing such complications were excluded, and all injection procedures were done under complete aseptic conditions.

The study findings revealed significant reduction in mean central macular thickness from 425.2 to 365.5 micrometers. Similar significant reduction in macular thickness was also reported in many studies. In one study, the central retinal thickness showed a considerable reduction from 498.9 at baseline to 370.4 micrometers at one month follow-up<sup>22</sup>. In another study carried out by Arevalo *et al.*<sup>21</sup>, the mean central macular thickness by OCT, among the studied 88 patients, was found to decrease from 387.0 at baseline to 275.7 at end of 16 weeks follow-up period. The mean decreases in central macular thickness after single intravitreal injection of 1.25mg of bevacizumab noticed after one month was about  $61.4 \pm 33.2$  micrometers<sup>22</sup>. In our study, the mean difference was very like that reported in the previous study. It was  $59.7 \pm 32.5$ .

In our study, stratified analysis by patients' characteristics were also performed and revealed significant reduction in the mean macular thickness after bevacizumab injection among patients less than 60 years, and male patients, and those with best corrected visual acuity at baseline  $\geq 0.1$ . These findings coincide with that reported in many previous studies<sup>16-18</sup>, and confirm the accumulating literature that young age, male gender and best corrected visual acuity at baseline as the most important prognostic factors after intravitreal injection of bevacizumab. Stratified analysis by reason of injection showed statistically significant reduction in the mean macular thickness among patients presented with DME, Macular edema secondary to BRVO, Neovascular glaucoma and among those patients presented with Macular edema secondary to CRVO. These findings were also reported in previous similar studies.<sup>17,18</sup>

The study findings found that 41 eyes showed  $\geq 10\%$ , and 18 eyes showed  $< 10\%$  decrease in macular thickness. Ateeq *et al.*<sup>20</sup> in their study included 54 patients who were submitted to intravitreal injection of bevacizumab, 43 Eyes (79.6%) showed  $\geq 10\%$  decrease in macular thickness from pre-injection thickness, 10 Eyes (18.5%) showed  $< 10\%$  decrease macular thickness post operatively after one month.

Macular thickness reduction, three months after bevacizumab, was analyzed in the present study by patients' diagnosis. More than ten percent reduction in macular thickness was found in 23 (38.9%) out of

35 DME patients, 5 (8.4%) out of 9 patients with PDR, and 5 (8.4%) out of 5 patients presented with PDR and VR, and 4 (6.7%) out of 4 patients with DME and PDR. The use of bevacizumab with success in treatment of diabetic macular edema is very beneficial for diabetic patients. DME is one of the major complications, leading to irreversible visual loss among diabetic patients, and up to 10% of diabetics develop it during their lifetime<sup>23</sup>. According to the Early Treatment Diabetic Retinopathy Study (ETDRS), focal laser photocoagulation reduces the rate of visual loss by 50% among these patients<sup>24</sup>. On the other hand, it is impossible to use complete macular grid laser in patients having media opacity like cataract, so there is a great need for an alternative or adjunctive treatment<sup>20</sup>. The usefulness of intravitreal injection of bevacizumab in these patients may help to reduce visual loss in patients with DME.

The biologically plausibility of the effectiveness of intravitreal injection of bevacizumab in treatment of these patients could be explained by the etiologic factor implicated in development of macular edema. Vascular endothelial growth factor (VEGF), discovered in 1989, secreted by normal retinal pigment epithelial cells as result of hypoxia is known to be significantly elevated in diabetic eyes<sup>25,26</sup>, particularly those eyes with proliferative diabetic retinopathy<sup>27</sup>. It is also observed that eyes with heavy macular leakage to have significantly higher VEGF concentration compared to eyes with less leakage<sup>28</sup>. Therefore, anti-VEGF treatments can be considered as an adjunctive treatment for DME<sup>29</sup>. Bevacizumab is a monoclonal antibody that binds to all kinds of VEGF and thus inhibiting its adverse effects<sup>1</sup>.

The second studied outcome parameter in this study was the visual acuity. At baseline, there were 38 eyes (64.4%) with best corrected visual acuity of  $\geq 0.1$  Decimal. Three months after intravitreal injection of bevacizumab, a significant improvement in patients' best corrected visual acuity by about 14% was detected in the studied eyes. Moreover, paired analyses have revealed that 9 (43%) out of studied 21 patients with baseline visual acuity  $< 0.1$  Decimal were corrected, and only one eye (7.7%) of 38 eyes with baseline visual acuity  $\geq 0.1$  Decimal was deteriorated. Costa *et al.*<sup>30</sup> have demonstrated significant dose-response changes in best corrected visual acuity at 3 months follow-up in their prospective, nonrandomized open-label study of 45 patients with ME and subfoveal CNV. The vision improved by +0.3 ETDRS line after a dose of 1.0 mg, by +0.6 line after 1.5 mg, and by +1.0 line after 2.0 mg of intravitreal injection of bevacizumab. In a case report study, a 69 years old woman with DME underwent an intravitreal injection of bevacizumab at a dose of 2.5 mg in her eye. There has been an improvement of her visual acuity to 20/400 one

month, and 20/200 four months after injection<sup>31</sup>. Another recent study has reported a highly significant improvement of visual acuity after intravitreal bevacizumab injection. The mean baseline acuity was 20/494 and the mean acuity at three months following injection was 20/295<sup>32</sup>. Over the years, many studies have documented the highly effective role of anti-VEGF treatment in preserving visual acuity in most eyes with proliferative neovascularization and age-related macular degeneration<sup>33-35</sup>.

In conclusion, the study confirmed the usefulness and short-term efficacy of intravitreal injection of bevacizumab in patients with macular edema of different causes, particularly those with diabetes. Intravitreal bevacizumab injection was found to significantly reduce the central macular edema and to improve the visual acuity of the studied eyes. Selection of patients submitted to this procedure is mandatory to obtain these required positive results. Apart from its efficacy, intravitreal injection of bevacizumab has also appeared to be relatively safe in the short-term with no cases of systemic or ocular complications have been reported in this case series follow-up study.

According to our knowledge, this study is the first to assess short-term outcome of intravitreal injection bevacizumab injection in Madinah medical centers. Moreover, and unlike other similar studies, the present study has stratified all analyses concerning the studied outcome parameters by patients' clinical and demographic characteristics. Though the above mentioned positive points, the nonrandomized nature of this study prevents any estimation of the long-term safety and/or efficacy of the studied procedure. However, the study findings are quite promising and suggest the need for further investigations with larger multicenter randomized studies.

#### Competing interests

The authors declare that there have no competing interests regarding the publication of this manuscript.

#### Limitations

The study was unable to score one-month OCT and there wasn't further follow up after three months. The OCT results were limited in vitreous hemorrhage.

#### Conclusion

The study confirms the accumulating evidence of the usefulness and short-term efficacy of intravitreal injection of bevacizumab.

#### Further Work

The study suggests the need for further investigations with larger multicenter randomized

studies and the need for increasing awareness about the importance of diabetes control and its impact in our region.

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## Does Clinical Training in Pediatrics Improve Med III Students' Approach to Children? A Cohort Study

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### Abstract

**Background & Objective:** Physical examination is the cornerstone for correct patient diagnosis. Examination of a pediatric patient requires additional skills related to patient-doctor interaction. Therefore, performing an accurate and complete physical examination of a child may be a challenging if not an impossible mission for unexperienced medical students during their pediatric internship. Having a pediatric-adjusted clinical approach might be the solution.

**Methods:** A Cohort study was done in our university hospital "Notre Dame des Secours". All Med III students<sup>27</sup> received a supplementary 3-hours presentation with instructional videos regarding pediatric physical exam (P/E) approach. This was followed by a Q/A session with a pediatric attending and 1-week rotation on the pediatric floor and pediatric ER. Pediatric residents supervised them during daily rounds and staff meetings. Students were afterwards asked to fill a questionnaire focusing on different pediatric physical exam skills. The same questionnaire was filled by the same medical students at the completion of their pediatric Med III scheduled rotation. The control group consisted of the Med III students<sup>29</sup> - who did not receive the supplementary presentation - after completing their pediatric rotation. Control group was asked to fill the same questionnaire. We used the "Statistical Package for the Social Sciences" (SPSS) version 22 as a statistics analysis tool.

**Results:** After comparing the two groups, 19.6 % and 39.3% OF Med III students in intervention group felt respectively that "if a child cries it is their fault" ( $p=0.023$ ) and that "the child's mother is always right until proven otherwise" ( $p=0.000$ ) vs 7.1% and 14.3 % in controls. Regarding the child's comfort, the intervention group learned that "if the child is ticklish, their own hands can be used to palpate the abdomen" ( $p=0.000$ ). However, questions regarding starting with ENT exam and using firm tone or skipping parts of examination were not significant ( $p=0.063$ ;  $p=0.150$  respectively). Intervention group medical students learned that using gowns and explaining all PE steps to the child may be a solution for better interaction ( $p=0.007$ ). In addition, leaving the child's underwear on or asking parents to leave the room ( $p=0.025$ ) can optimize intimacy. They can just observe their gait and musculoskeletal status in case of noncooperation ( $p=0.030$ ), and finally letting a child play with their medical tools can help gain their trust ( $p=0.003$ ). The rest of the results was not significant: "child is not a small adult" ( $p=0.237$ ), Adults and children should not be examined the same way ( $p=1.000$ ). "Trying to estimate a child's age" ( $p=0.073$ ) and "commenting on their choices of clothing" ( $p=0.055$ ). "Parents should not intimidate their children to answer questions nor answer for them" ( $p=0.087$ ).

**Conclusion:** We conclude that our supplemental training program did improve some aspects of student's pediatric PE skills. Students learned to implement new techniques to relax children and comfort them. The primary results are promising. A larger scale study should be done to better assess the advantages of implementing such a change in the Med III curriculum.

### Key Words

Physical Examination; Clinical Formation; Pediatric Approach; Pediatric Population

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### Introduction:

Physical examination (PE) is the cornerstone of correct patient diagnosis. It is a priceless tool that all medical students must master. During the average student's internship, the adult physical

examination is repeated numerous times, giving an opportunity to be learned and mastered. On the other hand, the pediatric physical examination is frowned upon and regarded to be hard without proper training.



Examination of a pediatric patient requires students learning additional skills related to pediatric patient-doctor interaction. Therefore, performing an accurate and complete physical examination of a child may be a challenging if not an impossible mission for inexperienced medical students during their pediatric internship.

Furthermore, a general course with topics handling clinical skills prior student's rotations enhances comfort levels among students before beginning rotations<sup>1</sup>, providing a needed boost for the student's performance.

In general, medical students are trained to use a "head to toe" technique, applicable for an adult physical examination, and are under the impression that this approach is age-independent. Having a pediatric-adjusted clinical approach training might be the solution.

### Materials and Methods:

We conducted a cohort study at our university hospital "Notre Dame des Secours" in Lebanon. All Med III students<sup>27</sup> received a supplementary 3-hour PowerPoint presentation with instructional videos regarding pediatric physical exam approach, covering topics such as starting with the "invasive" parts of PE while the child is still calm<sup>2</sup>. The spectrum of the pediatric population, being defined as birth to 21 years of age<sup>3</sup> is broad. Developmental stage-specific techniques could be implemented to tackle the first few challenging stages of life being newborns, infants, and children. Strategies covered students' general approach and adaptation to different situations<sup>4,5</sup> behavior towards children and gaining their trust<sup>4,5</sup> the use of age-specific strategies and techniques<sup>4,5,6</sup> how to perform an efficient organ system-directed PE<sup>4</sup> and how parents can play a positive role during the PE.

Baseline Characteristics		Med III Students									
		Intervention					Control				
		Mean	Min	Max	Total N	Count	Mean	Min	Max	Total N	Count
Age		23	22	25	27		24	23	26	29	
Gender	Male					14					16
	Female					13					13
Number of siblings		1	0	3			1	0	6		
Previous encounters with pediatric patients	No					9					0
	Yes					18					29
Level of relaxation during PE (1-10)		3					3				
Pediatrics as specialty	Peds not a possible specialty					21					25
	Yes, specialty					6					4
	Yes, subspecialty					0					0
Pediatrics as subspecialty	Peds not a possible subspecialty					24					26
	Yes, subspecialty					3					3

This presentation was followed by a one-hour Q/A session with a pediatric attending and 1-week rotation on the pediatric floor and pediatric emergency department. Pediatric residents supervised them during daily rounds and staff meetings. Students were afterward asked to fill a questionnaire focusing on different pediatric physical examination skills. The same questionnaire was filled by the same medical students at the completion of their pediatric Med III scheduled rotation. A control group consisting of Med III students (29) - who did not receive the supplementary presentation after completing their pediatric rotation, filled the same questionnaire. With a 95% confidence interval and 5% margin of error, we used the "Statistical Package for the Social Sciences" (SPSS) version 22 as a statistical analysis tool.

We used an Analysis of variance (ANOVA) to compare the two groups. Correlations were explored using Spearman's, Pearson's and McNemar correlations when fitting.

#### **Results:**

After comparing the two groups, 19.6 % and 39.3% of Med III students in the intervention group felt respectively that "if a child cries it is their fault" ( $p=0.023$ ) and that "the child's mother is always right until proven otherwise" ( $p=0.000$ ) vs 7.1% and 14.3 % in controls. Regarding the child's comfort, the intervention group learned that "if the child is ticklish, their own hands can be used to palpate the abdomen" ( $p=0.000$ ). However, questions concerning starting with ENT exam and using firm tone or skipping parts of examination were not significant ( $p=0.063$ ;  $p=0.150$  respectively). Intervention group medical students learned that using gowns and explaining all the PE steps to the child may be a possible solution for better contact ( $p=0.007$ ). In addition, leaving the child's underwear on or asking parents to leave the room ( $p=0.025$ ) can optimize intimacy. They can just observe their gait and musculoskeletal status in case of noncooperation ( $p=0.030$ ), and finally letting a child play with their medical tools can help gaining their trust ( $p=0.003$ ). The rest of the results was not significant: "child is not a small adult" ( $p=0.237$ ), Adults and children should not be examined the same way ( $p=1.000$ ). "Trying to estimate a child's age" ( $p=0.073$ ) and "commenting on their choices of clothing" ( $p=0.055$ ). "Parents should not intimidate their children to answer questions nor answer for them" ( $p=0.087$ ).

#### **Discussion:**

A published article by Soares *et al*<sup>8</sup> concluded that a medical student's exposure to pediatric topics in the preclinical period, especially in students with little to

no experience with the pediatric population, can boost their confidence and comfort levels, leading to a more relaxed approach in performing a pediatric physical examination during clinical pediatric clerkships. We can argue that a relaxed medical student, will be able to perform a thorough physical exam which would optimize his diagnostic potential. If the medical student successfully won the trust of the child he is examining, the child may be more cooperative.

A limitation of this study is the small population size and the monocentric approach.

The focus of this study is to assess the importance of a preclinical teaching program in pediatrics. Students acquired new knowledge regarding children's behavior, and appropriate strategies allowing them to handle different situations.

The study confirmed that almost everyone agrees that a child is not a small adult and should not be treated as one and that an adult approach, which a student is comfortable performing, cannot be applied to a child. Students did learn some key techniques in handling hard situations such as measures that can be taken to gain a child's full cooperation before starting the physical examination, and how to make a child more comfortable during a physical examination. Students also learned strategies to implement for the child not to feel neither exposed nor vulnerable. They also learned about the positive role that parents can play during their child's physical examination, and what they should do in case the child was uncooperative during a physical examination.

This training program could be essential in handling the pediatric population, alongside practical clinical experience, but the final goal is to efficiently implement this training in the medical curriculum, in a way to achieve all the learning outcomes.

#### **Conclusion:**

We conclude that our supplemental training program did improve some aspects of student's pediatric PE skills. Students learned to implement new techniques to make children relaxed and comfortable. The primary results are promising. A larger scale study should be done to better assess the advantage of implementing such a change in the Med III curriculum.

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## Defining the Role of the 'Future Surgeons: Key Skills' Course in The Surgical Curriculum

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### Abstract

The Royal College of Surgeons of Edinburgh 'Future Surgeons Key Skills' course aims to provide medical students and foundation (FY) doctors with a solid grounding in frequently practiced surgical skills. To evaluate its effectiveness and whether attendees benefited, an observational qualitative study of attendees' confidence was performed.

Attendees anonymously completed a five point pre- and post-course questionnaire rating their confidence in: gowning and gloving (GG), handling instruments (HI), handling sharps (HS), knot-tying (KT), simple suturing (SS), skin lesion excision (ESL), cyst excision (EC), wound debridement (WD), laparoscopy (LS) and diathermy skills (DS). Mean scores were calculated and a paired Student's t-test used for analysis.

One hundred and forty attendees completed the questionnaire. A significant improvement in confidence was observed in all components before attendees were divided into "early" (years 1-2), "intermediate" (years 3-5) and "advanced" (FY1 and FY2). Early attendees improved most in GG, HS, HI, LS and DS. Intermediate attendees improved most in KT, SS, ESL, EC and WD.

This study shows that attendees benefited overall and in each group. GG, HI and HS can be considered introductory skills, with the remaining skills intermediate based on the groups that most benefited. LS and DS are more difficult to class, probably due to differences in session structure or increased video game experience. A course focusing on GG, HI and HS would benefit early attendees. The 'Future Surgeons: Key Skills' course should focus on teaching intermediate attendees and act as a refresher for advanced attendees.

### Key Words

Future Surgeons; Key Skills; Surgical Assessment; Simulation; Students; Foundation Doctors; Surgery; Surgical Training

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### Introduction

The Key Skills course has been formed following the success of the well-known 'Basis Surgical Skills' (BSS) course. The BSS was established in 1994 following collaboration of all four royal colleges to introduce surgical trainees to safe and technically sound surgical techniques early on in their career. The Basic Surgical Skills course is specifically aim at FY1, FY2 and core trainee 1 doctors<sup>1</sup>.

The consultant led Royal College of Surgeons of Edinburgh, Future Surgeons Key Skills course was introduced to address a basic lack of structured surgical skill teaching to medical students with an interest in surgery. It has been running at the Christie Hospital, Manchester since January 2012. It aims to provide medical students of all years and foundation doctors a solid grounding in the following skills: gowning and gloving (GG), handling

instruments (HI), handling sharps (HS), knot-tying (KT), suturing (S), excising a skin lesion (ESL), excising a cyst (EC), abscess drainage (AD), wound debridement (WD), laparoscopic skills (LS) and diathermy skills (DS). It differs from the BSS in that it targets trainees at a more junior level, specifically medical students and foundation doctors<sup>2</sup>.

### Aims & Objectives

To evaluate the effectiveness and ascertain whether the attendees attained benefit and an improvement in their confidence pertinent to the skills learned on completion of the course.

To gain an understanding of why the attendees participated in the course and the perceived level of the suitability of the course for medical students and foundation doctors.

### Material and Methods

Attendees anonymously completed a five point Likert scale pre- and post-course questionnaire rating their confidence in each of the aforementioned skills (1 = not at all confident, 2 = not confident, 3 = somewhat confident, 4 = confident, 5 = very confident). A copy of both the pre- and post-course questionnaires are available in appendix 1 and 2. One hundred and forty attendees anonymously completed the questionnaire and their answers matched. Mean scores were calculated for each skill and compared pre- and post-course. They were divided into three groups. Medical students in years 1 and 2 were classed as 'early attendees', medical students in years 3-5 were classed as 'intermediate attendees' and foundation doctors were classed as 'advanced attendees'. The mean confidence ratings in each group were then compared for each skill to assess whether there were any differences between the cohorts. A paired Students t-test was performed to analyse the data. The questionnaire also included questions related to attendees' purpose to attend and perceived suitability of the course with space for elaboration. Attendees who were neither medical students nor foundation doctors were excluded from the study.

### Results

A total of 140 attendees participated in this study;

111 of whom were from the United Kingdom, 19 from International countries with 10 not stating their university of study. The questionnaires used in this study were taken from attendees who attended courses between January 2013 and June 2014.

The total number of early and senior attendees were 20 and 81 respectively; whilst there were 32 advanced attendees who attended the course. There were 7 non-medical attendees who were excluded from the study. Graph 1 shows the distribution of medical students and foundation doctors.

Of the remaining 133 questionnaires analysed, 55 were male, 64 were female with 14 attendees did not specify gender.

The average increase in mean confidence and p-value which was calculated using a paired Student's t-test showed the following results for each of the eleven skills (*Table 1*): GG (1.00,  $p<0.0001$ ), HI (1.50,  $p<0.001$ ), HS (1.04,  $p<0.0001$ ), KT (1.72,  $p<0.0001$ ), S (1.46,  $p<0.0001$ ), ESL (2.25,  $p<0.0001$ ), EC (2.20,  $p<0.0001$ ), AD (2.31,  $p<0.0001$ ), WD (2.10,  $p<0.0001$ ), LS (1.63,  $p<0.0001$ ) and DS (1.74,  $p<0.0001$ ). These results show that there is a significant improvement in each of the eleven skills taught at the course (*Table 1*).

Skill	Pre-course (mean)	Post-course (mean)	Difference (mean)	P-value
Gowning and gloving (GG)	3.45	4.45	1.00	$P<0.0001$
Handling instruments (HI)	2.89	4.39	1.50	$P<0.0001$
Handling sharps (HS)	3.50	4.54	1.04	$P<0.0001$
Knot-tying (KT)	2.44	4.16	1.72	$P<0.0001$
Simple suturing (S)	2.70	4.16	1.46	$P<0.0001$
Excising a skin lesion(ESL)	1.77	3.98	2.25	$P<0.0001$
Excising a cyst (EC)	1.69	3.86	2.20	$P<0.0001$
Abscess drainage (AD)	1.69	3.96	2.31	$P<0.0001$
Wound debridement (WD)	1.75	3.80	2.10	$P<0.0001$
Laparoscopy skills (LS)	2.22	3.85	1.63	$P<0.0001$
Diathermy skills (DS)	2.15	3.88	1.74	$P<0.0001$

**Table 1:** The Pre- and Post-course Feedback Mean and Difference of the Eleven Skills Taught on the Course

Skill	Attendee Group	Pre-course (mean)	Post-course (mean)	Difference (mean)	P Value
Gowning & gloving	Early	3	4.3	1.3	<0.0001
	Senior	3.4	4.4	1.0	<0.0001
	Advanced	3.8	4.7	0.9	<0.0001
Handling instruments	Early	2.8	4.5	1.7	<0.0001
	Senior	2.8	4.3	1.5	<0.0001
	Advanced	3.1	4.5	1.4	<0.0001
Handling sharps	Early	3.3	4.6	1.3	<0.0001
	Senior	3.4	4.5	1.1	<0.0001
	Advanced	3.8	4.6	0.8	<0.0001
Knot-tying	Early	2.6	4.1	1.5	0.0002
	Senior	2.4	4.2	1.8	<0.0001
	Advanced	2.7	4.3	1.6	<0.0001
Simple suturing	Early	2.7	4.0	1.3	0.0005
	Senior	2.6	4.2	1.6	<0.0001
	Advanced	3.0	4.3	1.3	<0.0001
Excising skin lesion	Early	1.8	4.0	2.2	<0.0001
	Senior	1.6	3.9	2.3	<0.0001
	Advanced	2.4	4.1	1.7	<0.0001
Excising Cyst	Early	1.8	3.9	2.1	<0.0001
	Senior	1.5	3.8	2.3	<0.0001
	Advanced	2.1	4.0	1.9	<0.0001
Abscess Drainage	Early	1.5	3.9	2.4	<0.0001
	Senior	1.5	4.0	2.5	<0.0001
	Advanced	2.3	4.1	1.8	<0.0001
Wound debridement	Early	1.7	3.7	2.0	<0.0001
	Senior	1.6	3.8	2.2	<0.0001
	Advanced	2.1	3.8	1.7	<0.0001
Laparoscopy	Early	2.0	3.9	1.9	<0.0001
	Senior	2.2	3.9	1.7	<0.0001
	Advanced	2.5	3.8	1.3	<0.0001
Diathermy	Early	1.5	3.7	2.2	<0.0001
	Senior	2.1	3.9	1.8	<0.0001
	Advanced	2.6	3.9	1.3	<0.0001

**Table 2:** Confidence Ratings of Early Attendees (n=20), Senior Attendees (n=71) and Advanced Attendees (n=32).

From Table 3, 121 of the attendees stated pre-course that they attended the course to learn new skills, 84 to develop skills in preparation for a career in surgery and 93 to enhance new skills. In addition, 105 of the attendees stated pre-course that they attended to improve their confidence and 96

attended to improve their portfolio or to obtain a certificate. No attendees did not know their reason for attending the course but 3 stated other reasons including 'preparation for elective' and 'refresher for surgery'.

Reason to attend	Number of attendees	Percentage (%) (n=133)
Learn new surgical skills	121	90.98
Enhance existing surgical skills	84	63.16
Improve confidence whilst attending theatre	93	69.92
Develop skills to prepare for a career in surgery	105	78.95
Improve your portfolio/ obtain a certificate	96	72.18
Don't know	0	0.00
Other	3	2.26

**Table 2:** Attendee Reasons for Attending the Course with Percentage of Total Attendees

The results from Table 4 show that 48 of the attendees had no experience of the skills taught prior to the course, only 7 had attended a formal course, 29 had attended surgical workshops whereas 19 had other experience. Of those that

listed 'other', comments included 'medical curriculum/university', 'theatre/hospital experience' and 'other courses'. 22 attendees had previous exposure through more than one of the experiences listed in the question.

Experience	Total number of attendees	Percentage (%)
Prior Experience	Yes 77 No 48 Didn't specify 8	Y 57.9 N 36.1
Formal Course	Yes 7	5.3
Surgical Workshop	Yes 29	21.8
Other	Yes 19	14.3
More than one of above	Yes 22	16.5

**Table 2:** Attendee Surgical Experience Prior to Attending the Course



Graph 2 shows attendees perceived that medical students in years 4 and 5 would benefit most from this course as well as foundation year 1 doctors. There was also a significant minority who perceived that the course would be suitable for a third year students and foundation year 2 doctors

### **Discussion**

When observing the attendees as a whole, the largest improvement was observed ESL, EC, and AD with all these parameters increasing by at least 2.10. This suggests that these skills are not widely taught (resulting in a low pre-course confidence) but relatively easy to learn (resulting in a high post-course confidence).

Less improvement (though still significant) was seen in the remaining skills which may indicate that the attendees found these difficult to learn despite previous experience or that the attendees were confident pre-course in these skills and this was enhanced by the course. GG, HI, HS, KT and SS all had a pre-course confidence mean of 2.44 or above and post-course mean of 4.16 or above suggesting that the former is true for these skills. LS and DS had an initial pre-course confidence mean of 2.22 and 2.15 with a post-course confidence of 3.85 and 3.88 respectively indicating that the latter applies to these skills.

When the mean confidence ratings were divided based on group (early, senior and advanced attendees), it was found that early attendees benefited most from GG, HI and HS. Senior attendees improved most in KT, SS, ESL, EC, AD and WD. Interestingly, early attendee confidence was most improved in LS and DS.

On this basis, it could be said that GG, HI and HS are basic skills. The results indicate that the least experienced cohort (years one and two) had a relatively low pre-course confidence but went on to improve the most when assessed post-course. The other groups had a better initial pre-course confidence level suggesting prior experience or that the skills are relatively basic for their level of knowledge.

KT, SS, ESL, EC and WD were found to benefit senior attendees the most. This may suggest that this group of skills are most appropriate for attendees with some basic surgical skills experience (as most third, fourth and fifth year students would expect to have gained) and that these skills are relatively easy to learn.

Although popular opinion may expect otherwise, the fact that early attendee year attendees

improved most in LS and DS implies that these skills are relatively easy to learn and gain confidence in. Another more likely theory could be based around the way the skills were taught. Both of these skills were more theory based with basic skill tasks given. The other skills involved demonstration and specific skill sets. This might explain why the least experienced students gained the most confidence and this is corroborated by the fact all three groups had a very similar post-course confidence. A further explanation may lie with the fact these skills rely on the use of technology. One cross-sectional analysis concluded that increased video game experience in surgeons resulted in faster completion of laparoscopic tasks with fewer mistakes when compared to those with less gaming experience<sup>3</sup>. This has also been found in studies with veterinary students and was recently supported by a large literature review<sup>4,5</sup>. Another study also suggested that younger groups spend more time playing video games<sup>6</sup> thus providing anecdotal evidence to explain why the early attendees benefited most in LS and DS. However, the study did not collect data on the age of each cohort or the amount of time spent playing video games. It is therefore difficult to conclude whether these skills are best suited to a particular group.

Given the groups that benefited most from each skill, there is scope for an 'introductory surgical skills' course aimed at early attendees, teaching them GG, HI and HS. The key skills course may be best served by teaching senior and advanced attendees, providing a group with a similar initial skill set and therefore enabling more focused teaching. There is suggestive evidence that if this course is introduced for early attendees, they would go on to benefit more in the Key Skills and Basic Surgical Skills courses in the future. This is based on a study that showed that people attending the Key Skills course performed better in the Basic Surgical Skills course than those who did not.

The attendees participating in the Future Surgeons Key Skills course have clearly defined reasons to attend. However, there were 121 attendees who sought to learn new skills and 84 who sought to build on existing skills. This implies that there was some overlap in the skills already possessed by the students and supports the idea that some of the skills would be considered basic to the attendees whereas others may be viewed as intermediate or more advanced. The course is also relevant to both the surgical setting and career development as a large majority also sought to improve theatre skill (93), gain skills to prepare for a career in surgery (105) or gain a certificate/develop their portfolio (96).

The majority of the attendees had had some exposure to surgical skills either through attending a formal course or via a surgical skills workshop pre-course. However, the proportion of attendees who did not have prior experience was also relatively high indicating that the course serves to teach new skills and consolidate existing skills. Of those that selected 'other' for prior experience, only 9 attendees cited experience through their university/medical curriculum. This represents just 6.77% of the cohort and suggests that more should be done to introduce to surgical skills into the UK medical curriculum. This evidence is supported by another study performed at King's College using a similar style of assessment. It found that students at their university have very little experience in knot-tying and suturing and 96% would advocate the introduction of surgical skills into their curriculum prior to starting surgical placements<sup>7</sup>. Our study assesses a greater number of components and the cohort comes from a broader population which may indicate that surgical skills would benefit the medical curricula nationally. Perhaps an option to select 'university/medical curriculum' in future questionnaires would enable more accurate assessment of exactly how much experience attendees have from university.

Who the attendees thought the course would be most suited for loosely follows the same patterns as those who actually attended. The majority of attendees thought that medical students in years 4 and 5 as well as FY1 doctors would benefit the most. The fact that this correlates well with the cohort who improved the most across the greatest number of skills suggests that the course teaches a lot of new skills to early attendees and served as a refresher for senior attendees. Some also selected year 1, year 2 and FY 2 doctors which would indicate that these groups still perceive benefit from the course although this may be more dependent on the experience of the attendee as an individual. For example, a third year student with no experience could potentially be overwhelmed by surgical skills that they are completely unaware of or have had no experience in.

The confidence of the students for the post-course questionnaires was taken immediately on completion of the course. It has not been observed whether the improvement in confidence is short-term or whether they benefit over a longer period of time. Further study after a sustained period of time on the same cohort would determine whether attendees benefit is longstanding. Other limitations of this study are those that apply to all observational studies; bias, confounding, chance and cause<sup>8</sup>. Given the statistical significance of the data and the fact that the only outcome measure relate directly to

the course, there seems little evidence for any of the aforementioned limitations.

### **Conclusion**

There was a significant improvement in confidence in each of the skills taught on the course. Hence, this course is effective in achieving its aim to deliver basic surgical skills to all the attendees. The difference in mean improvement of some tasks suggests that some of the skills are more advanced than others and that some are easier to learn than others for attendees. Based on the results, GG, HI and HS could be considered 'introductory' skills. KT, SS, ESL, EC, AD and WD can be viewed as 'intermediate' skills whereas laparoscopy and diathermy are more difficult to class due to either session structure or gaming experience. More research is required to determine why early attendees benefited the most from LS and DS. It follows that the introductory skills would be most appropriate for early attendee medical students as an introduction to these skills or as a refresher for senior and advanced attendees. The Key Skills course should continue but would be better suited to senior and advanced attendees. Anecdotal evidence suggests that attendees of a new introductory surgical skills course would subsequently benefit even more in the Key Skills and Basic Surgical Skills course.

The attendees themselves have a clear aim for attending the course, primarily to learn new skills, gain more experience as well as developing their portfolio and preparing for careers in surgery. The course also serves to teach new skills and consolidate existing skills. Furthermore, this course establishes that whilst many attendees had had prior experience, a very small proportion had gained this from experiences in university. This study advocates that formal surgical skills teaching should be introduced into the medical curricula in the UK.

It would be worthwhile to perform another questionnaire after a significant period of time (for example 3-6 months) to determine if these levels of confidence are maintained. This may be logistically difficult as attendees come from all over the UK and from abroad in some cases so postal/email questionnaires may have a low response rate.

### **Disclosure**

The authors do not have any conflicts of interest or financial ties to disclose.

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# Implementing Innovative Medical Education Strategy at Moi University College of Health Sciences: Are There Enough Resources?

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## Abstract

**Introduction:** Innovative medical education strategy is arguably one of the most important innovations in medical education in the last century. The evident benefits of this strategy and the changing face of medicine and medical education have led many institutions including those in resource poor settings to consider the adoption of the strategy. However, experts are uncertain about how successful it will be in such settings, as literature on the implementation of the strategy in resource-poor settings appears to be inadequate. This study sought to find out if there are enough resources to successfully implement innovative medical education strategy at Moi University College of Health Sciences.

**Methods:** Participants were drawn from students, lecturers and administrators; all being users of innovative medical education strategy used to teach and learn in the College of Health Sciences 274 students, 65 lecturers and 9 administrators were recruited into the study. Self-administered questionnaires were used in data collection. This questionnaire utilized a five point forced Likert scale (1-Totally disagree, 2-Disagree, 3-Not Sure 4-Agree and 5-Totally Agree). The questionnaire also consisted of an open-ended section to comment on the strategy process and contents.. Cronbach's alpha, median and inter-quartile range (IQR) was calculated in SPSS 22.

P-value less than or equal to 0.05 was taken as statistically significant. Ethical approval was obtained from the Institutional Review and Ethics Committee (IREC) of Moi University and Moi Teaching and Referral Hospital.

**Results:** The response rate among students was 250 (91%) out of 274, Lecturers' response was 90% of which 65 of them returned the questionnaires out of the total sample of 72. For the administrators they all returned their questionnaires being 100% response of the sample of 9 participants. Seventy eight percent of the administrators said that the resources were partially enough with 1 (11.1 %) saying that they were enough, All the lecturers were in agreement that the resources were partially enough.

**Conclusions:** Both lecturers and administrators agreed that the College had resources which were partially enough. This inadequacy of teaching materials has affected SPICES model, which it is now moving towards mixed method. The resources which were categorized as being partially enough were lecture halls, LCD projectors, computers, internet, technicians and vehicles for COBES centers and field trips. This is short of WFME Standards of requiring courses to be funded; supply of more teaching materials should be availed.

## Key Words

Medical School; Perception; Problem Based Learning; Students

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## Introduction

We can define innovative teaching and learning method as a program or series of events which the teacher implements to assist the student to remain focused on what that individual is doing. It stimulates the students' ability to engage in problem-solving activities that make a student an expert in his/her area of concentration. This process makes a

student an active learner and the teacher a facilitator as opined (Zhu, Wang, Cai, & Engels, 2013).

Innovative approach to learning was facilitated by the growth of technology in 19<sup>th</sup> century (Hmelo-Silver & Barrows, 2006) argues that the introduction of instructional media in teaching

facilitated various innovative opportunities. To meet the needs of innovative teaching and learning method, majority of the institutions who adopted it opted for problem-based teaching and learning method. Filho argues that problem-based teaching and learning method became increasingly popular in educational institutions because of actively being able to engage students in constructing knowledge (Rezende-Filho, da Fonseca, Nunes-Souza, da Silva Guedes, & Rabelo, 2014). Personally in a classroom, but only via internet as opined by (Deniz, Kesan, & İzgiol, 2013) Innovative method of teaching and learning adopted by medical colleges then is the problem-based learning. Koh *et al* opines that problem-based learning have been introduced to improve the quality of graduating health professionals. They argue that graduates taught using problem-based learning method are more competent and systematic compared to the ones trained using traditional lecture method (Koh, Khoo, Wong, & Koh, 2008).

This arose from the need to train doctors who can serve in the 21<sup>st</sup> Century; doctors who are equipped with skills that enable them respond to medical problems they face, able to adapt to the unknown future problems they will encounter. Doctors who can form teamwork with other health professionals to solve community's health challenges. This was to be achieved through training medical students in research methods to enable them research for solutions to community's health challenges with other health professionals. They were taught how to do self-directed learning of which they would use as a means of getting solutions to community's health problems after graduation (Levenson, Atkinson, & Shepherd, 2010).

### Methods

This research is a descriptive cross-sectional study design; which utilizes both qualitative and quantitative method of data collection. Participants were drawn from students, lecturers and administrators; all being users of innovative medical

education strategy used to teach and learn in the College of Health Sciences 274 students, 65 lecturers and 9 administrators were recruited into the study. Self-administered questionnaires were used in data collection. This questionnaire utilized a five point forced Likert scale (1-Totally disagree, 2-Disagree, 3-Not Sure 4-Agree and 5-Totally Agree). The questionnaire also consisted of an open-ended section to comment on the PBL process and contents. Data entry was done in SPSS version 22. Cronbach's alpha, median and inter-quartile range (IQR) was calculated in SPSS 22 for Windows. P-value less than or equal to 0.05 was taken as statistically significant. Ethical approval was obtained from the Institutional Review and Ethics Committee (IREC) of Moi University and Moi Teaching and Referral Hospital.

### Results

The response rate among students was 250 (91%) out of 274, Lecturers' response was 90% of which 65 of them returned the questionnaires out of the total sample of 72. For the administrators they all returned their questionnaires being 100% response of the sample of 9 participants. Seventy eight percent of the administrators said that the resources were partially enough with 1 (11.1 %) saying that they were enough, All the lecturers were in agreement that the resources were partially enough.

### Availability of Resources for Implemented innovative Medical Education Strategy

The objective of this study was to identify resources available for implementing innovative Medical Education Strategy in the College of Health Sciences. The success of any implemented program highly depends on the availability of resources to be used in running the program. Among the resources needed are buildings for classrooms and office accommodation, instructional media such as laptops, computers, chairs and books. There is need to have vehicles to transport students during field trips and COBES projects.

LCD Projectors	Total	Functional	Non-functional
SOM	27	20	7
SPH	7	6	1
SON	6	6	-
SOD	5	2	3
<b>Total</b>	<b>45</b>	<b>34</b>	<b>11</b>
<b>Computers</b>			
SOM Computer Lab	20	-	20
Library Computer Lab	20	20	-
<b>Total</b>	<b>40</b>	<b>20</b>	<b>20</b>
<b>Vehicles</b>			
Bus, mini-buses & others	22	7	15

**Table 1:** Checklist for Teaching Materials and Space

1. LCD Projectors, Computers and Vehicles
2. Laboratory re-agents (chemicals) stocking is always below 30%.
3. Internet connectivity is available only, but not always.
4. For a vehicle to be functional, it must be in good mechanical condition with all stickers required by Kenya government for vehicles carrying passengers.
5. Space:
  - Old Library has an area of 821 square meters.
  - Skills Laboratory has an area of 153 square meters.

To ascertain the number of LCD projectors and computers, the researchers visited the custodians and counted them physically. For the re-agents laboratory technicians from the four schools totaled stock card entries for 6 months and averaged them. This was done in the presence of the researcher, as opined by (Laitenberger, El Emam, & Harbich, 2001) that checklists can be used to compare the actual and that confirm the reality on the ground. To ascertain space, the researcher measured the two rooms and calculated the area in square meters.

Both Old Library and Skills Laboratory were chosen because they are used to teach combined groups of the four schools.

Majority of students agreed that lecture halls, technicians, chairs and books were moderately enough. But LCD projectors, computers and vehicles for COBES were seen to be lacking where students scored 50, 42 and 79 respectively by stating that they totally disagree with the availability of these teaching materials, as per Table 2.

	TD	D	NS	A	TA
Do you have enough lecture halls	40	58	39	78	35
Do you have enough LCD Projectors	50	80	47	45	28
Do you have enough Chair and Books	42	53	41	78	36
Do you have enough Technicians	23	49	59	85	34
Do you have enough Vehicles for COBES	79	58	58	42	13

1. TD = Totally Disagree 2. Disagree 3. NS = Not sure 4. Agree 5. TA = Totally Agree

**Table 2:** Students' View on Availability of Resources for Implementing Innovative Medical Education Strategy

A test of reliability was conducted on the scales used in the questionnaire. The result of the coefficient alphas indicated satisfactory reliability. According to DeVellis Reliability Guidelines (1991:15), a Cronbach alpha coefficient over 0.7 implies respectable reliability. In this study, Cronbach alpha coefficients of lecture halls, chairs and books, technicians, LCD projectors and COBES vehicles was 0.77. A value over 0.7 is seen as an acceptable value for Cronbach's alpha; a value substantially lower indicates an unreliable scale. In this study, the Cronbach alpha coefficient of the 5 scales was over 0.7 that was seen as a good

indicator of their reliability and high acceptability.

By use of calculated mode, students ranked the need of vehicles for COBES and field trips being the most wanting. The next needy area was the instructional media such as LCD projectors, computers and internet, as per Table 3.

By use of a calculated mode; all the lecturers were in agreement that the lecture halls, LCD, whiteboards, laptops and teaching rooms were inadequate at the College of Health Sciences as per Table 4.

Students Statistics					
	Do you have enough Lecture Halls	Do you have enough LCD Projectors	Do you have enough Chairs and Books	Do you have enough Technicians	Do you have enough Vehicles for COBES
N	250	250	250	250	250
Mode	4	2	4	4	1

**Table 3:** Students' Response about the Availability Teaching Materials



Lecturers				
		Enough	Partially	Few
Are there enough lecture halls		5	54	6
Are there enough, LCD, Whiteboards & Laptops		7	41	17
Is there enough room for teaching in the hospital		3	34	38
Lecturers Statistics				
		Are there enough Lecture halls	Are there enough LCD Whiteboards Laptops	Is there enough room for learning in the hospital
N	Valid	65	65	65
Mode		2	2	2

**Table 4:** Lecturers' View on Availability of Resources for Implementing Innovative Medical Education Strategy

### Administrators

Administrators 7 (78%) said that the lecture halls and laboratories were partially enough with 1 (11%) saying that they were enough, they were in

agreement that the LCD whiteboards chairs and Laptops were partially available at 5 (56%) and 1 (11%) saying they were enough; as per Table 5.

Lecture halls and laboratories			
	Frequency	Percent	%
Enough	1		11
Partially	7		78
Very Few	1		11
Total	9		100
LCD whiteboards chairs and Laptops			
	Frequency	Percent	%
Enough	1		11
Partially	5		56
Very Few	3		33
Total	9		100

**Table 5:** Administrators' View on Availability of Resources for Implementing Innovative Medical Education Strategy

### Discussion

The objective of this study sought to identify resources available for implemented innovative Medical Education Strategy in the College of Health Sciences. The success of any program depends on the availability of resources. Among the resources needed included classrooms, office accommodation and instructional media such as laptops, projectors, computers and books, as well as vehicles to transport students during field trips and COBES.WFME Standards indicates that "...allocate resources necessary for the implemented curriculum". So for the implemented SPICES model

of teaching and learning, resources have to be availed (Karle, 2006).

### Student's perception on availability of resources

Among the students, majority agreed that College of Health Sciences had moderately enough lecture halls, technicians, chairs and books. This had been made possible by Medical Education Centre and Conference (MECC) and the new building for Public Health, Dentistry and Nursing, commonly referred to as PDN building (College of Health Sciences, 2016).

Students also identified COBES and field trips as the most ineffective programs due to lack of sufficient vehicles. This particular problem has also been registered in reports by (Chang *et al.*, 2011; Jinadu, Ojofeitimi, & Oribabor, 2000) and the Federal Democratic Republic of Ethiopia (2015:2). To alleviate this problem, more vehicles need to be procured for COBES and field trips. The University administrators and lecturers must see COBES as part of the curriculum that requires full support like others courses in the curriculum. However, if programs such as COBES and field trips are seen as extra-curricular activities, procurement of the needed vehicles will not be given the priority it deserves. This view has been shared by Kang'ethe, Kiguli-Malwadde, Jinadu and the Federal Democratic Republic of Ethiopia in their publications (Jinadu *et al.*, 2000; Kang'ethe, 1998; Kiguli-Malwadde *et al.*, 2006). This is contrary to the WFME Standards which indicates that "...allocate resources necessary for the implemented curriculum". COBES has not been facilitated to the level of others courses; yet it is the course that exposes students to community's health problems (Karle, 2006).

Students unanimously agreed that the College should acquire more LCDs, projectors, computers and improve internet speed and access. The provision of instructional media should be based on the population of the students (Ericsson, 2008). Students reported that there were few instructional media materials and that some which were there, had been rendered non-functional due to wear and tear and poor maintenance. Poor electrical connectivity was another factor stated by the students. Skocherlaks has observed that most modern instructional media rely on electric power (Skochelak, Barley, & Fogarty, 2001). It is important to also consider that some of the requisite instructional media needed for medical training are expensive to procure in adequate quantities (Kei, 2011).

Some areas had internet connectivity but suffered from frequent interruptions due to either non-payments or maintenance schedules on electric lines. These findings concur with those of Skocherlaks and Hamad in their studies (Hamad, 1999; Skochelak *et al.*, 2001).

Overcrowding was caused by high student-lecturer ratio, which could not allow the College to split the classes into a manageable level of 7 to 10 students per tutorial group. This pointed to the need to recruit more lecturers, a view that has also been urged by Prince and Felder (Prince & Felder, 2006). The reviewed literature showed that overcrowding in Medical Colleges in developing countries is caused by the lack of sufficient funding to these

institutions. The rate at which high schools are churning out students ready to join Medical Colleges does not match that of government funding to expand available utilities. Governments are faced with high population growth, and little sources of generating revenue; hence the lack of funding to existing Medical Colleges; and this agrees with observations by Abraham (Abraham & Azaje, 2013).

Overcrowding reduces the effectiveness of for implementing innovative Medical Education Strategy because the little resources available for this program will be strained, students have to crowd around a projector of which some will not understand the ongoing teaching. This then forces the lecturer to improvise, which ends up having to teach using mixed method other than SPICES model, as observed by Wood (Wood, 2003).

Concerning the study objective; resources are available for the implemented innovative Medical Education Strategy, but they are all depleted and even the functional ones are faced by interruption of electricity and overcrowding of students.

#### **Lecturer's perception on availability of resources**

Most lecturers noted that the College had inadequate lecture halls, chairs, computers, books, LCD projectors and laptops. However, they noted that most of the available equipment was non-functional. They attributed this to the fact that some of this equipment is expensive to replace, as opined by Kei in his PhD Thesis (Kei, 2011).

Lecturers suggested that all teaching and learning facilities need improvement; that when teaching aids are not availed, teaching is compromised. They argued that the insufficiency of the equipment needed was one reason many lecturers were shifting from SPICES model teaching and learning method back to the lecture one. This is against WFME Standards that teaching and learning should be funded (Karle, 2006). When lecturers are not facilitated, then proper teaching cannot take place, this finding was in agreement with an observation made by Veitia *et al* in their study (Veitia, McCarty, Kelly, Szarek, & Harvey, 2001).

Most of the lecturers said that they needed training in SPICES model of teaching and learning. Some of them said they had been trained in their undergraduate using SPICES model. Others had had a chance to be trained in the use of SPICES model, either through workshops they had attended or by voluntarily joining first-year students during lessons on how to use SPICES model of teaching and learning during first year students' orientation. The

approach taken by lecturers in joining first-year students in order to learn SPICES model is not the best way to train new staff. This approach reduces SPICES model to lecture method; because students will participate during the course but the lecturer/administrator will observe, take notes and leave.

Lecturers pointed out that they had not been provided with teaching materials such as laptops and the internet. Even the few functional laptops could not be fully utilized because of electric power interruptions. Lecturers who are not provided with teaching materials and trained on the use of instructional media are overtaken by their students in the area of technology. Lonka suggests strongly that lecturers should always be availed with instructional media and training on how to apply them (Lonka, 2013).

Availing resources for the implemented innovative Medical Education Strategy model, lecturers have been hired, but they are not facilitated to teach. The little resources available have been overstretched by overcrowding.

#### **Administrator's perception on availability of resources**

The College administrators pointed out that lecture halls were inadequate. They also noted that laptops, projectors, computers and internet were not enough. They attributed the problem to inadequacy to funding for the College. They observed that stocking the College with teaching and learning materials was costly. It is contrary to WFME Standards that courses should be funded, and should be noted that when courses are not funded, teaching changes from SPICES model to lecture method (Karle, 2006).

The respondents emphasized the need for sufficient office spaces and teaching rooms. The College has grown from a population of 40 students to the current one of 1200 as indicated in Moi University College of Health Sciences. It has grown 30 times from its initial population, yet the teaching and office spaces have not grown to in corresponding rate. The lecturers also posited that the skills laboratory was not well equipped. The administrators attributed this to the high cost of equipping innovative Medical Education Strategy.

The College has acquired some instructional media such as laptops, projectors and the internet, but these are few, insufficient and inefficient. Coupled with the inefficiency of some equipment due to constant power interruptions it disrupts learning. According to the respondents, these power interruptions were caused by scheduled maintenance and disconnection due to non-

payment.

Students, lecturers and administrators reported that College vehicles were not enough to facilitate excursion activities. Concerning the second objective, therefore, on the state of resource availability for the implementation of innovative Medical Education Strategy, it was found out that resources were inadequate; a thing that goes contrary to WFME Standards which urges Medical Schools to avail resources for teaching all courses (Karle, 2006).

#### **Conclusions**

Both lecturers and administrators agreed that the College had resources which were partially enough. This inadequacy of teaching materials has affected implementing innovative Medical Education Strategy, which it is now moving towards mixed method. The resources which were categorized as being partially enough were lecture halls, LCD projectors, computers, internet, technicians and vehicles for COBES centers and field trips. This is short of WFME Standards of requiring courses to be funded; supply of more teaching materials should be availed.

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# Improving Medical Students' Preparedness for Post-Graduate Practice: A Supplementary Teaching Programme

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## Abstract

**Background:** Evidence shows that medical graduates feel unprepared for their foundation years, particularly when managing acutely unwell patients.

**Aim:** To improve the confidence and feeling of preparedness amongst final year medical students for post graduate practice and specifically the role of the foundation doctor.

**Method:** Using a Likert scale, students were asked to rate their confidence with regards to different areas of practice. 90% of students felt unprepared and 40% felt that medical school had not adequately prepared them for post-graduate practice; particularly on call shifts. Following this we designed an 8 session teaching programme specifically to improve confidence surrounding the role of the foundation year 1 doctor on call. Using didactic lectures, low fidelity simulation and small group teaching sessions covered clinical tasks and non-technical skills.

**Results:** Whilst students remained anxious, 50% felt more prepared and confident. Students felt the course addressed areas not readily covered in their formal teaching.

**Conclusion:** There is a need for further teaching focussed around on-call tasks specific to the role of the foundation doctor to be incorporated into formal teaching programmes. This will reduce anxiety around this transition and ensure foundation doctors feel both adequately prepared and clinically supported.

## Key Words

Education; Training; Quality; Safety; Curriculum Design

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## Introduction

There is evidence that many medical graduates feel unprepared for their foundation years; particularly with regards to managing acutely unwell patients and the non-technical skills that this complex process involves<sup>1</sup>. The GMC conducted a survey in 2009 which found that 1 in 10 UK medical graduates felt poorly prepared, leading to concerns as to whether new graduates are safe to practice<sup>2</sup>. One study found there was a 6 % increase in patient mortality when new doctors start work in the NHS<sup>2,3</sup>.

There is some evidence that students from Problem-based learning (PBL) courses feel better prepared for their foundation years compared to students from more traditional courses, particularly in relation to practical and communication skills<sup>4</sup>, however further research has identified that students from multiple medical schools and course types continue to feel unprepared for their foundation years<sup>5</sup>.

Perceived preparedness can influence the behaviour

of new graduates and the potential impact upon patient safety and emotional wellbeing of graduates is of paramount importance<sup>6</sup>. Medical educators must ensure that specific areas of weakness are targeted to ensure this transition is effective, students feel supported and high standards of care are maintained.

## Aim

To implement a course to directly improve final year medical students confidence with regards to starting FY1 (Foundation Year 1). To equip them with essential skills for the role of the FY1 on call, specifically the assessment and management of an acutely unwell patient, time management, task prioritisation, communication and handover.

## Method

### Survey and focus groups

We conducted a survey amongst 10 final year medical students from Newcastle University on placement at a District General Hospital for their final year of undergraduate study. We aimed to identify any concerns they may have with regards to

starting their foundation years and highlight specific areas of weakness that they felt they needed to improve upon prior to starting their Foundation Year 1. In addition to small focus groups, a questionnaire was conducted using the Likert Scale and students were asked to rate their confidence with regards to a variety of tasks essential for their foundations years.

### **Survey Results**

70% of students felt anxious about commencing FY1 and 90% felt unprepared. Only 40% felt that medical school had adequately prepared them for starting FY1. Areas causing most anxiety included managing acutely unwell patients, interpreting x-rays and procedural skills. Only 20% felt confident interpreting x-rays and no student felt confident placing a nasogastric tube or performing an arterial blood gas sample.

Non- technical skills such as the process of handover and asking for help were also of significant concern (*Figure 1*). Only 40% of students felt confident asking for help and only 30% stated they felt confident with the process of handover. 50% felt they were aware of what information was required to be placed in a discharge letter.

### **Developing a programme**

Based on these results, we designed an 8 session teaching programme over a period of 16 weeks. The programme started in January, 6 months into their final academic year. These sessions supplemented their formal final year teaching on areas where students lacked confidence and not readily covered during their traditional medical school course. In addition to the 8 teaching sessions, themes ran through all the sessions and were built upon as the course progressed, specifically designed to improve confidence during on call shifts including; time management, task prioritisation, the process of handover and communication. Sessions were taught using variety of methods including didactic lectures, small group work and low fidelity simulation.

### **Teaching Sessions**

- Session 1: ABG interpretation (using cases including respiratory and metabolic disorders)
- Session 2: Practical prescribing (relevant to the role of FY1 on call including analgesia,

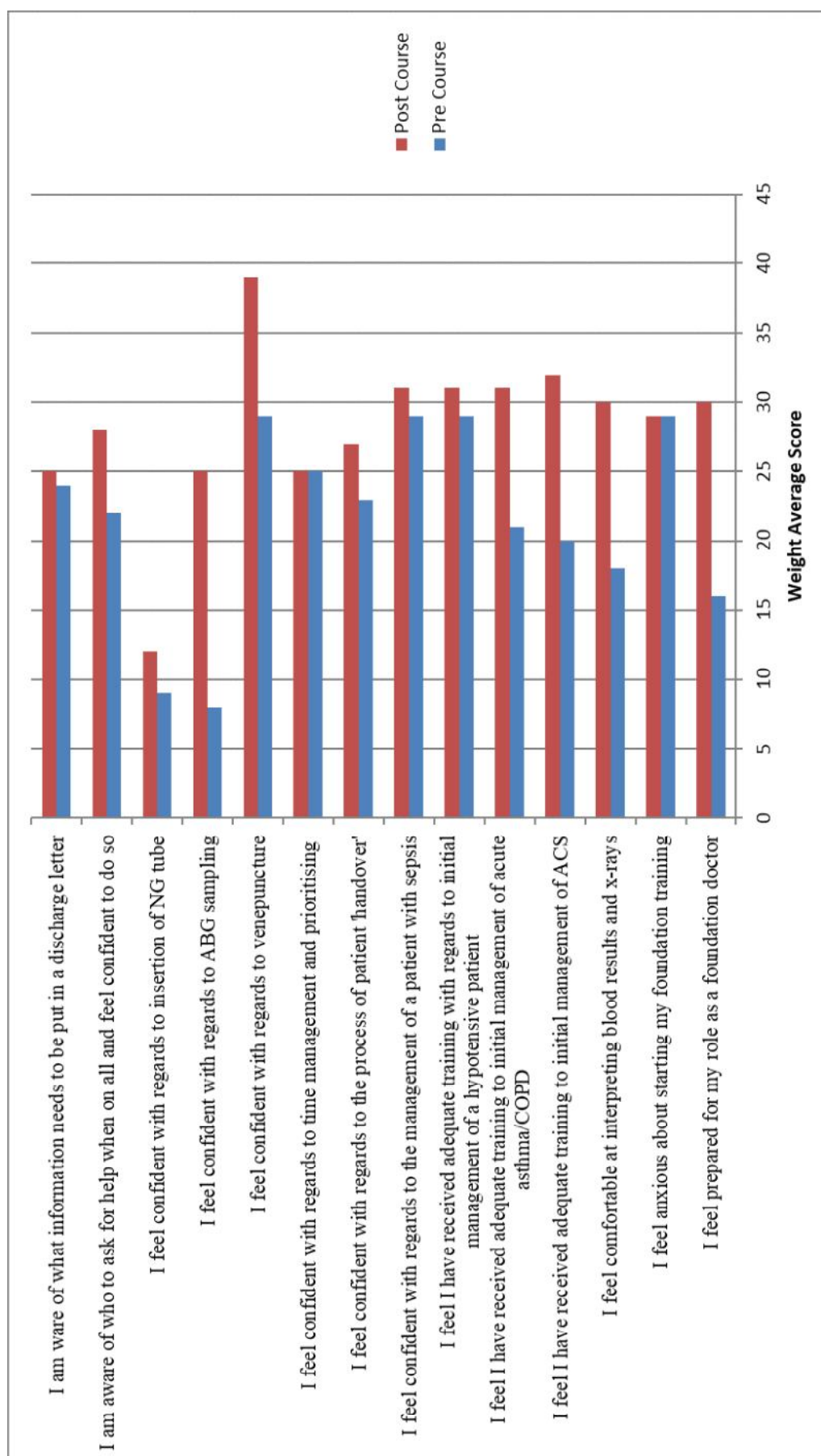
antibiotics, fluids, insulin, warfarin, electrolyte disturbances)

- Session 3: Radiology ( interpretation of common chest x-rays and abdominal x-rays).
- Session 4: Blood test interpretation ( commonly encountered issues on call such as rising inflammatory markers, abnormal liver function tests, acute kidney injury, electrolyte disturbances and markers such as D-dimer and troponin)
- Session 5: Acutely unwell surgical patient simulations (acute abdomen) including task prioritisation and handover/ referring to another speciality.
- Session 6&7: Acutely unwell medical patient simulations (asthma exacerbation, acute coronary syndrome including ECG interpretation, septic shock and GI bleed) including task prioritisation and handover/ asking for help from a senior.
- Session 8: Clinical signs teaching relevant to acutely unwell medical patients.

### **Results**

Over the 16 week course, students gained confidence, with 50% feeling significantly more prepared and confident with regards to their role at the F1 on call. 80% felt confident asking for help and knew who to ask for help as opposed to 40% prior to the start of the course. 80% felt confident with regards to the process of handover; a 30% increase compared to the pre-course survey.

The chart below (*Figure 1*) shows a calculated weighted average score for each point; 4= strongly agree, 1= strongly disagree. This demonstrates a significant increase in confidence in most areas, particularly in terms of their preparedness for FY1 and important non-technical skills including, handover and the process of asking for help; particularly reassuring in terms of improving patient safety. There was also a significant improvement with regards to managing acutely unwell patients, procedural skills and interpreting x-rays. Interestingly, students remained very anxious with regards to starting FY1 and there is no demonstrated improvement in confidence with regards to time management and task prioritisation. Further research is required to explore this further.





### **Qualitative Feedback Comments**

What specific areas do you feel you have gained confidence in since undertaking this course?

- "Interpreting bloods & x-rays – thank you!"
- "Using the SBAR handover tool and escalating concerns"
- "Blood interpretation, A-E assessment and X-rays"
- "Prescribing common drugs/fluids"
- "Handover and being helpful on a ward/ understanding my future role as an F1"
- "Thanks to the teaching I am confident in my abilities and think it will help me quickly settle in as an F1"
- "There wasn't any specific area but has generally helped a lot by acting as extra practice alongside our regular teaching"
- "Communication, A-E assessments and interpreting bloods/x-rays"

### **Discussion**

Students felt unprepared for their foundation years and experienced significant anxiety prior to this course, 6 months before commencing their foundation year 1. Students expressed particular concerns regarding the acute management of patients, interpretation of x-rays and procedural skills. Interestingly, students felt confident with regards to managing sepsis and hypotension prior to starting this course, but felt less confident managing acute coronary syndrome, exacerbations of chronic obstructive pulmonary disease and asthma.

Following this course there was improvement in confidence in most areas. Unfortunately, our results show that there was no demonstrated improvement in confidence with regards to task prioritisation or handover and students remained anxious with only 50% feeling prepared and 80% feeling anxious.

One possible reason for this continued anxiety and feeling of being unprepared is the time of year in which the survey was repeated, just prior to commencing their FY1. However, at this point students have completed final year and passed their final exams and therefore, should feel confident and capable of performing FY1 duties.

### **The solution?**

The findings of this small study correlate with previous research conducted amongst new graduates. Since the report by the GMC in 2009 there appears to have been little improvement. Anxiety amongst medical students and foundation doctors is widely reported<sup>7</sup> and this cohort of students at the interface between university and

significant responsibility in their first year of practice are a vulnerable group<sup>8</sup>.

Burnout is a common problem in the UK amongst new graduates and has the potential to have a negative impact upon patient safety<sup>9</sup>. If we do not take targeted action, there could be a substantial impact upon patient safety as well as doctors' mental health and wellbeing with a subsequent impact on recruitment and retention.

Lachish<sup>9</sup> found that good support for foundation doctors promoted work place satisfaction and encouraged retention of doctors. Research has found that longer periods of shadowing significantly reduced levels of anxiety surrounding the transition from student to doctor<sup>1,11</sup>. Students valued most a period of shadowing<sup>12</sup>.

There is a need to better prepare medical students for their FY1. Our study suggests this could be achieved with more targeted teaching, aimed at providing them with the specific skills they require as well as improving their confidence and feeling of preparedness. Perhaps a prolonged period of internship attached to a ward post exams may be of benefit, which would provide an opportunity for students to gain hands on experience in an apprenticeship like role?

### **Limitations**

There was noticeable improvement in procedural skills including arterial blood gas sampling and nasogastric tube insertion; areas not directly covered during this course. This therefore leads to the question: was this course directly responsible or would students have achieved this level of self-confidence and feeling of preparedness via their formal teaching programme? Qualitative feedback was overwhelmingly positive and would suggest otherwise. This course was felt to be of significant additional value by students, and results correlate with previous research in this area, where more hands on experience positively influenced perceived preparedness<sup>5</sup>.

A further possible limitation is that the results are based on students self- perception of their ability and skills rather than objective assessment. However, previous research found that students self - perception of their ability was inline with the opinion of their supervisor<sup>13</sup>.

### **Conclusion**

Following this course there was evidence of improved confidence amongst the final year medical students with regards to most areas. Despite this course however, students remained anxious with

regards to commencing their foundation years. Further research is needed to explore whether similar courses are directly responsible for this improvement in confidence and there is a need for further research to identify why despite this additional focussed teaching programme, a significant number of students still feel unprepared. Subjective evidence however, demonstrates that students felt this course was of added value and our findings correlate with data collected from across the UK. Feedback was overwhelmingly positive and students gained confidence in areas specific for the role of the FY1 on call, not readily covered in their formal teaching programme.

In this small but positive study, we have highlighted a need for further teaching and experience focussed on on-call tasks specific to the role of the FY1 in order to ensure foundation doctors feel supported and adequately prepared for post-graduate practice. Ideally, this should be incorporated into formal teaching programmes, with particular emphasis on acute care. Further research is required to identify when in the traditional teaching programme this course would be best placed.

#### Main messages

- There is significant anxiety amongst final year medical students with regards to starting their foundation years.
- Students are particularly concerned about on call shifts and managing acutely unwell patients.
- A teaching programme designed specifically to address on call issues and common tasks can improve confidence
- There is a need to incorporate teaching specific to the role of the foundation doctor into formal medical school teaching programmes.
- Further research is required to identify the most appropriate teaching methods to prepare doctors for post-graduate practice and when within their academic year this is best achieved.

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# The Course of the Disease in Patients with Multidrug Resistant Tuberculosis with Depression

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## Abstract

**Aims:** Despite research advances in the microbiological and clinical aspects of MDR-TB, research on the psychosocial context of MDR-TB is limited and less understood and requires more intervention and interpretation. Our study aims to determine the course of the disease in patients with multidrug-resistant tuberculosis with depression.

**Methods:** The data of 45 patients with chemo-drug resistant tuberculosis, who belonged to 4<sup>th</sup> treatment category were examined. Patients were interviewed using the HADS scale and the reliability of the differences in qualitative indices between groups was determined by Fisher's exact test.

**Results:** It was determined that the proportion of patients among the persons who were treated in the 4<sup>th</sup> category for the first time and received anti-tuberculosis drugs for a duration of more than 4 months, was greater in the 1<sup>st</sup> group 1: 5 patients (62,5 %) versus 3 persons (11,1 %) in the 2<sup>nd</sup> group,  $p < 0,01$ . So, depression mostly affects patients, who treated for a longer time.

**Conclusions:** From the obtained data it is shown that drug users and patients who treated more than 4 months have psychological problems that complained after specific therapy side effects. In patients with functional disorders, depression is a reason for diseases course severity.

## Key Words

Multidrug-Resistant Tuberculosis; Depression; Psychological Stress; Infectious Disease; Microbiology

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**Introduction:** The long duration of treatment, toxicity and lack of treatment options, adversely effect the physical and mental well-being of multidrug-resistant tuberculosis (MDR-TB) patient. Regardless of advancement in the microbiological and clinical aspects, research on the psychosocial context of MDR-TB is limited and less understood, requiring more intervention and interpretation. The emergence of mental disorders in patients with multidrug-resistant tuberculosis (MDR-TB) are due to the same risk factors for their disease development, namely being stress, family and financial reasons. The impact of tuberculosis as a socially dangerous disease has been progressing due to side effects from the treatment for a longer period of anti-TB medicines and fear of treatment failure, as well as due to the social isolation of patients. Amongst all psychiatric disorders, depression is widely prominent in patients with MDR-TB. The global burden of MDR-TB is estimated to be around 60% in countries like India, China, and Russia<sup>1</sup>. Due to the high transmission

rate, illiteracy, poor knowledge and inability to afford the treatment from private practitioners makes the disease contagious especially in high density communities<sup>1,2,3,4,10,11</sup>. The perception of psychological stress is obscure but it is largely defined as a state of emotional suffering with a variety of symptoms like anxiety and depression<sup>5</sup>. Psychological stress is the major cause of mortality and individuals having high stress die 25 years earlier than normal population<sup>6</sup>. The poor prognosis is due to the long duration of treatment and drug toxicity<sup>7</sup>, causing resistance and this psychological distress also complicates the treatment of MDR-TB<sup>8,9</sup>.

## Aim

Our study aims to determine the course of the disease in patients with multidrug-resistant tuberculosis with depression.

## Material and methods

45 patients with chemo-drug resistant tuberculosis, who belonged to 4<sup>th</sup> treatment category were

examined. Patients were interviewed using the HADS scale and were divided into 2 groups. The first group included 10 people who scored 8 or more points on HADS scale, who were predisposed to severe depression. The group consisted of 6 men (60,0 %) and 4 women (40,0 %), with a mean age of  $39,2 \pm 2,3$  years. The 2<sup>nd</sup> group (comparison group) consisted 35 patients who scored less than 8 points on the HADS scale. The number of men in the comparison group was 27 (77,1 %), women – 8 (22,9 %), the mean average age of patients was  $38,5 \pm 1,8$  years. Both the groups were represented by gender and age ( $p < 0,05$ ).

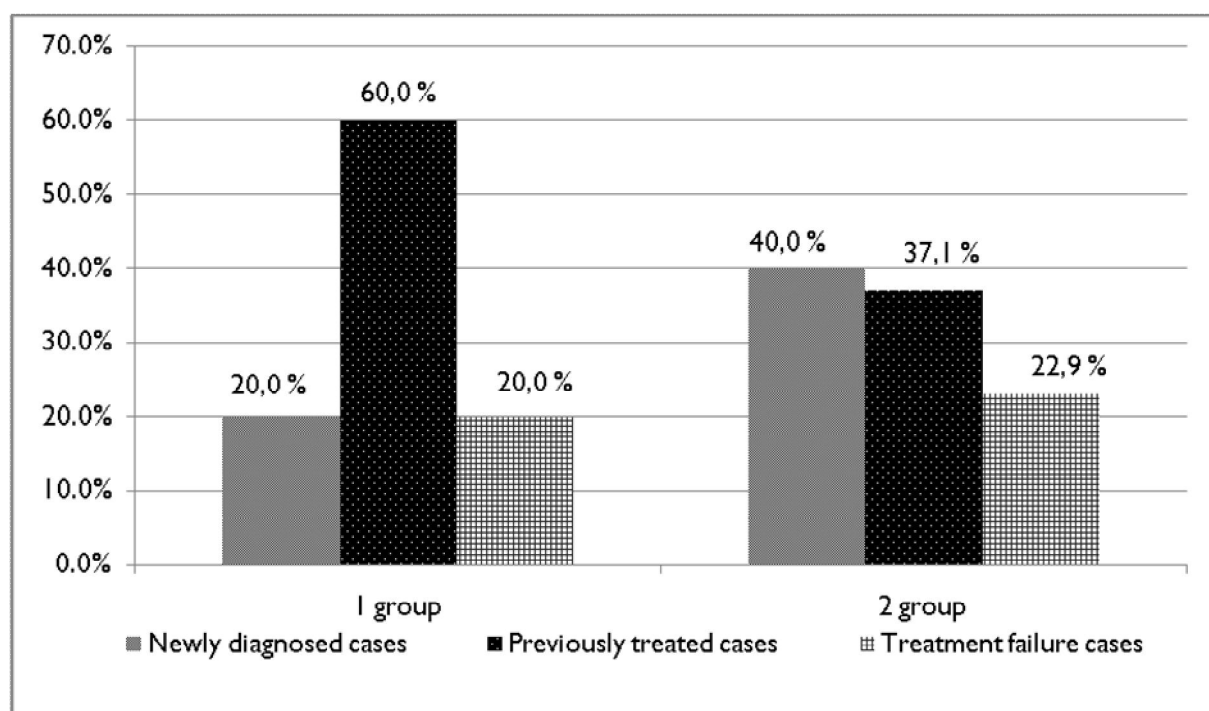
The statistical analysis and the differences between groups were performed using the STATISTICA® for Windows 6.0 (Stat Soft Inc., AXXR712D833214FAN5). The reliability of the differences in qualitative indices between groups was determined by Fisher's exact test. The value of the reliability indicator of the difference between groups for the level of statistical significance ( $p$ ) was

taken to be less than 0,05.

### Results and Discussion

About 1/5<sup>th</sup> of patients in both groups (20,0 % in the 1<sup>st</sup> and 22,9 % in the 2<sup>nd</sup>) were treated repeatedly after the failure of the first course of anti-tuberculosis therapy. It was determined that the proportion of patients among the persons who were treated in the 4<sup>th</sup> category for the first time and received anti-tuberculosis drugs for a duration of more than 4 months, was greater in the 1<sup>st</sup> group 1: 5 patients (62,5 %) versus 3 persons (11,1 %) in the 2<sup>nd</sup> group,  $p < 0,01$ . So, depression mostly affects patients, who treated for a longer time. It may be because of drugs side effects, long conversations with other patients who have poor treatment outcomes, or a feeling of total loneliness.

According to the tuberculosis case and their type, the groups of patients did not differ statistically and were not significant (Figure 1).



**Figure 1:** Tuberculosis Cases and Their Types in the Patient's Groups

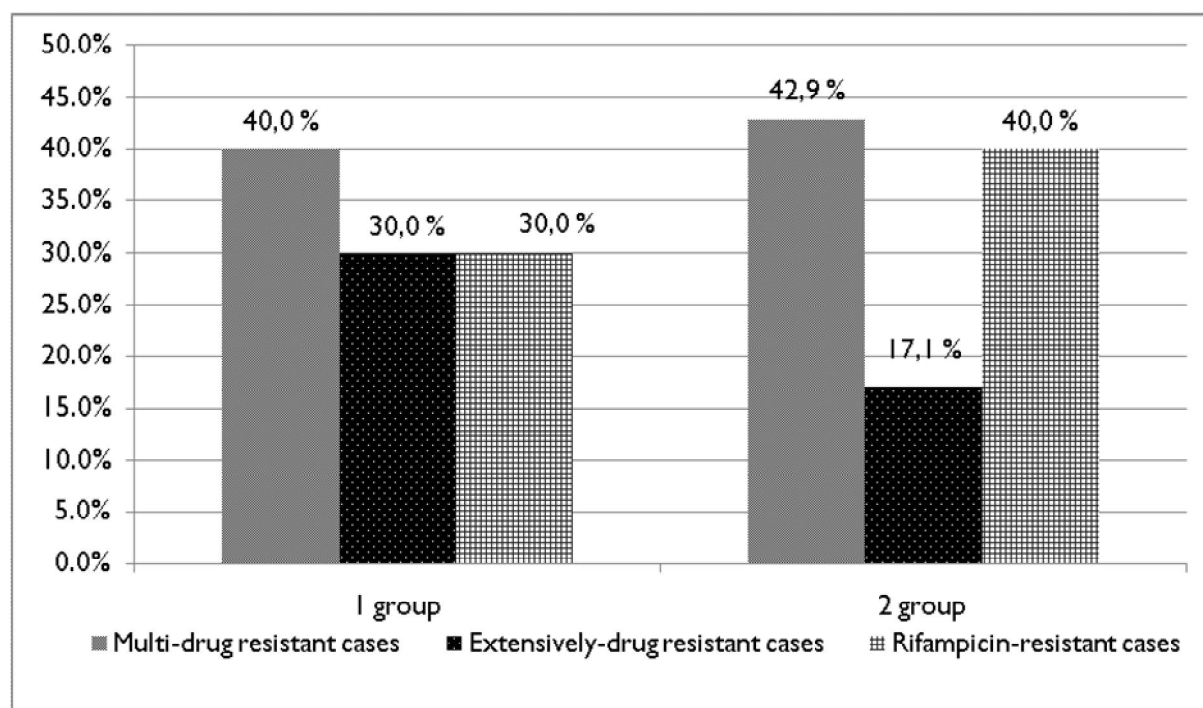


Figure 2: Chemo-Drug Resistant Cases Types in Patient's Groups

So, there were no differences found between the groups in types of tuberculosis cases and in types of drug resistance cases.

4 patients of 1<sup>st</sup> group (injecting drugs) drug addicts (40,0 %), only 1 patient (2,9 %) in the 2<sup>nd</sup> group was a drug addict,  $p < 0,01$ . The proportion of patients with HIV/AIDS co-infection was greater among the patients in the group 1: 4 (40,0 %) patients in the 1<sup>st</sup> group versus 3 (8,6 %) in the 2<sup>nd</sup> group,  $p < 0,05$ . According to the other concomitant diseases (diabetes mellitus, viral hepatitis, bronchitis), the groups did not differ significantly. The higher proportion of drug addicts among MDR-TB patients with depression may be explained because of narcotic drug using and psychological problems, associated with them.

Most patients in both the groups had bacterial secretion: 9 patients (90,0 %) in 1<sup>st</sup> group and 32 (91,4 %) in the 2<sup>nd</sup> group. Massive bacterial secretion was observed in 4 (40,0 %) 1<sup>st</sup> group patients and in 18 (51,4%) – of 2<sup>nd</sup> group,  $p > 0,05$ . In 1 patient from the 2<sup>nd</sup> group, extrapulmonary tuberculosis was diagnosed. All the remaining patients had pulmonary lesions. Disseminated pulmonary tuberculosis occurred in 3 patients from the 1<sup>st</sup> group (30,0 %) and in 12 (34,3%) – from the 2<sup>nd</sup> group, infiltrative – in 6 patients (60,0 %) from the 1<sup>st</sup> group and in 17 (48,6 %) – from 2<sup>nd</sup> group. In 1 patient from the 1<sup>st</sup> group, there was fibrous-cavernous pulmonary tuberculosis, whereas, in 6 patients of the 2<sup>nd</sup> group there was caseous pneumonia and fibrocavernous tuberculosis,  $p > 0,05$ .

The proportion of patients with pulmonary destruction was almost the same in both groups: 80,0 % of patients in the 1<sup>st</sup> group and 85,7 % in the 2<sup>nd</sup> group, the average size of the cavities in the 1<sup>st</sup> group patients was  $3,3 \pm 1,1$  cm, in 2<sup>nd</sup> group patients –  $2,8 \pm 0,4$  cm,  $p > 0,05$ .

More distinct functional disorders were registered in patients of the 1<sup>st</sup> group: according to the indicators like external respiration, failure of ventilation of 2<sup>nd</sup> and 3<sup>rd</sup> degree were diagnosed in 5 (71,4 %) 1<sup>st</sup> group of patients and 9 (26,5 %) 2<sup>nd</sup> group patients,  $p < 0,05$ .

So, there were not differences in clinical forms and radiological changes, but there were more patients with depression in patients, who had more severe failure of ventilation, because of the impact of functional disorders on quality of life of patients.

Adverse drug reactions took place in 7 patients (70 %) from 1<sup>st</sup> group and in 22 (62,9 %) – from the 2<sup>nd</sup> group,  $p > 0,05$ . Half of them were associated with clinical changes: in 5 patients (50 %) from 1<sup>st</sup> group and in 17 (48,6 %) – from 2<sup>nd</sup>,  $p > 0,05$ . In 5 cases in 1<sup>st</sup> group (50 %) and in 6 (17,1 %) in 2<sup>nd</sup> group side effects weren't cured,  $p < 0,05$ . So, not cured side effects worsened disease course and quality of patient's life, that's why there were more patients with depression among such persons.

Many studies have been conducted to depict the course of the disease in patients with multidrug-resistant tuberculosis with depression.

Fentie Ambaw *et al* 2017<sup>17</sup>, conducted a cross sectional study on 657 participants. They used PHQ-9 (Patient Health Questionnaires) scale to calculate depression. He suggested that incidence of depressive symptoms is a usual manifestation of tuberculosis. He also stated that female sex, old age are positive aspects and level of education, social support are negative aspects for the occurrence of depression.

Mrinalini Das *et al* 2014<sup>18</sup>, conducted a retrospective cohort study on 45 patients with 7 having depressive symptoms. They specified that routine administration of mental health evaluations by trained staff can help in determining and managing the depression signs during MDR-TB treatment. They also recommended steady nursing of mental health position by clinical staff.

Arshad Javaid *et al* 2014<sup>19</sup>, did a cross sectional study in 289 people of Pakistan. In this study they stated that continuous monitoring of patient's mental health status is important. Educating patients and their family members helps in proper management of a patient's condition during entire illness.

In our study we state that Depression affects patients with MDR-TB mostly if they are drug addicts ( $p < 0.01$ ) if they had a ventilatory failure of 2<sup>nd</sup> and 3<sup>rd</sup> degree ( $p < 0.05$ ), uncured adverse drug reactions ( $p < 0.05$ ) and if they were treated for more than 4 months ( $p < 0.01$ ). It means that drug users and patients who were treated for more than 4 months have psychological problems that complained after specific therapeutic side effects. In patients with functional disorders, depression is a reason for diseases course severity. Thus, such patients with MDR-TB should be undergoing evaluation for depression and need an additional therapeutic management.

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## Rare Cases of Pneumatosis Intestinalis and Hepatic Portal Venous Gas without Bowel Ischaemia

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### Abstract

**Introduction:** Pneumatosis intestinalis and presence of hepatic portal venous gas are traditionally recognised as ominous signs, often associated with intestinal ischaemia. However, it had also been found that it is associated with other pathologies.

**Cases review and case series:** Pneumatosis intestinalis is reviewed in this article and two patients who presented with this condition are discussed. The salient related literature is also reviewed.

**Conclusions:** Pneumatosis intestinalis and hepatic portal venous gas findings on CT do not always signify mesenteric ischaemia requiring surgical intervention with emergency laparotomy. Decision to operate should not be made solely on the basis of CT findings. Consideration should be broadened to include other potential diagnoses.

### Key Words

Pneumatosis Intestinalis; Hepatic Portal Venous Gas; Bowel Ischaemia

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### Introduction

Pneumatosis intestinalis and presence of hepatic portal venous gas are traditionally recognised as ominous signs, often associated with intestinal ischaemia. Patients may usually require laparotomy due to the risk of fatal outcome if left untreated.<sup>1</sup>

The incidence of pneumatosis intestinalis in the general population is around 0.03% based on autopsy series<sup>2</sup>; however, the number of cases seen appear to be increasing, most probably due to increased sensitivities of computed tomography (CT) technology.<sup>3-5</sup> Consequentially, findings of pneumatosis intestinalis and hepatic portal venous gas are increasingly being identified in a spectrum of conditions, both surgical and non-surgical.<sup>6,7</sup>

In current literature, evidence for the attribution of pneumatosis intestinalis and hepatic portal venous gas to a cause other than bowel ischaemia remains scarce.<sup>8</sup> McGregor A *et al* reported a case of a patient found to have both pneumatosis intestinalis and hepatic portal venous gas, but yielded negative result for ischaemic bowel following an exploratory laparotomy.<sup>1</sup> Lisa MH *et al* give examples in their review of various medical and surgical conditions associated with secondary causes of pneumatosis intestinalis and hepatic portal venous gas seen on

CT imaging.<sup>9</sup> Amongst life-threatening conditions such as ischaemic colitis, consideration is given to benign associations such as pulmonary diseases, systemic complications of rheumatological diagnosis, iatrogenic causes such as certain medications, and various intestinal disorders.

The benign and life-threatening causes of secondary pneumatosis intestinalis are tabulated overleaf.

Shawn *et al*<sup>6</sup> reports four cases of pneumatosis intestinalis with different spectrum. Two of these cases were managed conservatively. The first of these patients underwent CT which reported evidence of pneumatosis intestinalis and portal venous gas. This patient was discharged from the hospital without a definite diagnosis. The second patient had a background history of CREST (scleroderma with subcutaneous calcinosis, Raynaud phenomenon, oesophageal dysfunction, sclerodactyly, and telangiectasia) and chronic intestinal pseudo-obstruction with bacterial overgrowth. This patient again was treated conservatively with bowel rest and was discharged without any complications.

The third case involved a patient with background history of ulcerative colitis, admitted with diffuse

Benign Causes of Secondary Pneumatosis Intestinalis					
Pulmonary	Intestinal	Iatrogenic	Medications	Systemic	Transplant
Asthma	Pyloric Stenosis	Barium enema	Corticosteroids	Scleroderma	Bone marrow
COPD	Peptic Ulcers	Jejunioileal by-pass	Chemotherapy agents	Systemic lupus	Kidney
Cystic Fibrosis	Pseudo-obstruction	Jejunostomy tubes	Lactulose	AIDS	Liver
Pulmonary Fibrosis	Enteritis	Post-surgical anastomosis	Sorbitol	Rheumatoid arthritis	Cardiac
PEEP	IBD	Endoscopy			Lung
Life-Threatening Causes of Secondary Pneumatosis Intestinalis					
Intestinal Ischaemia		Toxic megacolon		Ingestion of corrosive agents	
Mesenteric vascular disease		Trauma		Intestinal obstruction/strangulation	
Collagen vascular disease		Organ transplantation		Inflammatory conditions	

**Table 1:** Causes of Pneumatosis Intestinalis, adapted from Lisa MH et al.

abdominal pain cramping in nature and associated with bloody stool. This patient was initially treated conservatively, however deteriorated and was advised to undergo proctocolectomy and ileal J-pouch-to-anal canal anastomosis with loop ileostomy. In this patient, the CT findings demonstrated extensive pneumatosis coli of the ascending colon and a pneumoretroperitoneum extending superiorly into the porta hepatis at the level of the inferior vena cava and duodenum. The last patient in this case series was a patient with background history of COPD who had a coronary bypass surgery and suffered from pulmonary complications and worsening of sepsis. A CT scan demonstrated extensive colonic pneumatosis, an air-fluid boundary in the superior mesenteric vein, copious portal venous gas, and bilateral renal infarcts. Treatment was withdrawn after discussion with the patient's family.

#### Review of Cases:

We are reporting two cases of patients with extensive abnormal CT findings of pneumatosis intestinalis and hepatic portal venous gas, with consideration of their clinical presentations and outcomes.

#### Case 1:

A 74 year old gentleman with a background history of advanced dementia, myocardial infarction, hypertension and hypercholesterolaemia was admitted with a 4 day history of generally felling unwell with several episodes of vomiting of dark green content. There was no history of

haematemesis, rectal bleed or melena. Upon clinical examination the patient had a soft and mildly distended abdomen and generalised tenderness. No hernias or masses were identified.

Initial investigations demonstrated a dehydrated patient with a urea of 20.1 mmol/L and a normal full blood count. Venous blood gas showed a pH was 7.49 with a lactate of 2.5 mmol/L. Chest x-ray was unremarkable and abdominal x-ray showed multiple distended small bowel loops.

The initial impression was small bowel obstruction. After initial resuscitation, the patient had a CT scan the same day, which was reported as:

"Generalised ischaemia of bowel and stomach with air seen in the stomach and bowel wall. Air is also seen in left intrahepatic portal vein. This raised the high suspicion of perforated appendix and secondary bowel obstruction with mural ischaemia." (Figures 1-3)

Despite the extensive CT report, the patient was not offered any surgery due to his multiple comorbidities and the fact that he was clinically stable. The patient opened his bowels without any problems. He experienced intermittent spiking of temperature and tachycardia, however his abdomen continued to improve throughout the stay in the hospital.

A follow up CT scan performed four days after hospitalisation showed: "Persistent distension of

small bowel loops without convincing evidence of pneumatosis intestinalis, and persistent stomach distension without any evidence of intramural gas. Previously described gas in portal vein had almost completely disappeared. Two collections were noted in right lower abdominal quadrant and right hemi-pelvis measuring 5.1 x 8.1 x 8.5cm and 5.3 x 5.2 x 10cm, and had progressed since CT four days ago."

The patient was started on combination of nasogastric feeding and total parental nutrition due



**Figures 1-3:** CT findings Demonstrated Air within Stomach, Bowel Walls and Intrahepatic Portal Vein

to poor oral intake.

A further CT scan was performed eighteen days from admission which showed: "Gas in stomach wall and bowel had now resolved. Gas previously seen in intrahepatic portal vein had also now resolved. Collections previously seen in right lower abdomen tracked to the right psoas muscle resulting in psoas abscess."

CT guided drainage was proposed; however the patient was considered high risk for sedation, therefore this therapeutic option was abandoned. The patient was treated with intravenous antibiotic instead.

The patient acquired a few nosocomial infection such as hospital acquired pneumonia, peripherally inserted central catheter (PICC) line infection and urinary tract infection. These were treated with the appropriate antibiotic.

One month following admission, a fourth CT scan showed: "Right iliac fossa abscess and psoas abscess reducing in size and resolving pneumonia."

Seven weeks following admission, the patient was considered to have had significant clinical improvement and nasogastric feeding was stopped.

The patient underwent another CT scan on the 53<sup>rd</sup> day of admission which showed: "Significant reduction in right sided psoas abscess."

The patient was discharged after two months of hospitalisation and had a final CT scan two months post discharge which showed complete resolution of previous collections.

The conclusion from the case was pneumatosis intestinalis and hepatic portal venous gas unrelated to bowel ischaemia.

#### **Case 2:**

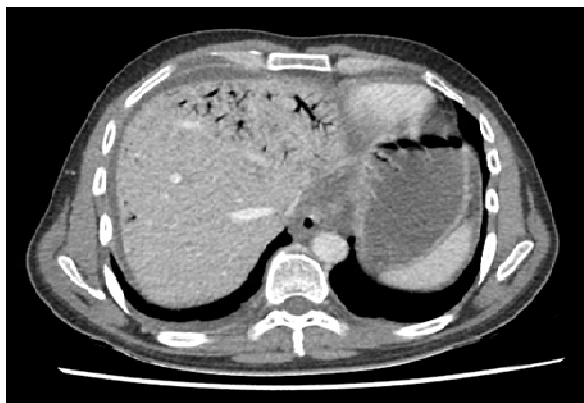
A 52 year old gentleman presented with a three day history of generalised abdominal pain, several episodes of dark brown vomitus, and passing black tarry stools. The patient denied any rectal bleeding and was otherwise previously fit and well, with past history of schizophrenia and epilepsy. Examination demonstrated a distended abdomen without guarding, with evidence of widespread tenderness and sluggish bowel sounds. All observations were within normal parameters, with exception of tachycardia at 140/min.

Initial investigations revealed raised inflammatory markers (white cell count  $18.2 \times 10^9/L$  and neutrophil count  $15.3 \times 10^9/L$ ). Liver and renal profile were normal. An arterial blood gas revealed

pH of 7.51 and normal lactate (1.0 mmol/L). Plain abdominal radiograph demonstrated multiple dilated small bowel loops.

The patient was commenced on initial resuscitation with intravenous fluid, antibiotic, and catheterisation. An urgent CT of abdomen and pelvis was reported as:

"Pneumatosis of bowel walls; air within the stomach wall and portal venous system; bowel necrosis



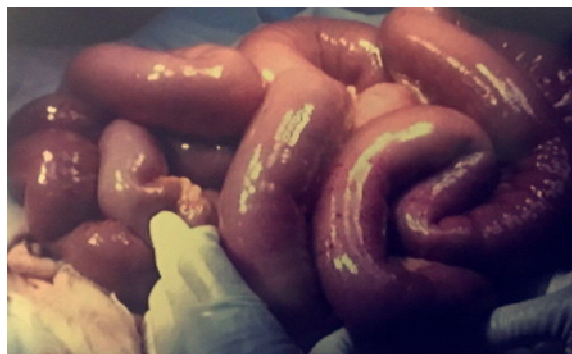
**Figures 4-5:** *Pneumatosis of Bowel and Stomach Walls*

throughout." (Figures 4-5)

A P-Possum score showed mortality at 43.3% and morbidity at 96.9%. In light of the CT findings and potential for fatal outcome left untreated, the patient was consented and taken to theatre to undergo an emergency laparotomy.

Remarkably, intra-operatively the small bowel was found to be well perfused with no signs of ischaemia

and there were no free air noted. The ascending and transverse colon were found to be distended,



**Figures 6:** *Intra-operative Findings of Healthy, Well Perfused Bowel with Intact Mucosa*

and a collapsed descending colon. (Figure 6)

Post-operatively the patient received ward-based care and was treated for surgical ileus, and did not require any intensive care input.

Oesophageoduodegastroscopy (OGD) was done to investigate the melena and haematemesis and was reported as normal. He was discharged from hospital after approximately three weeks of ward level treatment of surgical ileus.

### Conclusion

Pneumatosis intestinalis and hepatic portal venous gas findings on CT do not always signify mesenteric ischaemia requiring surgical intervention with emergency laparotomy. Decision to operate should not be made solely on the basis of CT findings. Consideration should be broadened to include other potential diagnoses. Further retrospective observation studies should be conducted to improve understanding of the differential diagnoses which could attribute to such findings on CT scans.

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# A Study Evaluating the Awareness of International Medical Students About the Evolution and History of Medical Terminologies

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## Abstract

The consolidation of key medical terminologies is an arduous, yet vital, task for numerous medical students. Many of the terminologies used in common medical practice are derived from Greek and Latin, which poses an added challenge in the task of memorising such terminologies; amongst others, one of the reasons being that these classical languages are no longer routinely taught in the primary, secondary, or higher education settings within the United Kingdom. The relationship between the knowledge of Greek or Latin which medical students possess and their understanding of medical terminologies is an essential area of enquiry within the field of medical education and clinical practice. This study endeavours to examine if acquisition of the Greek or Latin languages during primary and/or secondary school education can benefit medical students. In order to investigate this, a survey was carried out on 218 medical students from 28 countries worldwide who were attending the Doctors Academy 7th International Medical Summer School at the University of Manchester, United Kingdom. The survey was conducted on the final day of the week-long event. The results indicate that medical students have a limited understanding of the Greek or Latin origin of medical terminologies and that, as a result, their ability to comprehend the meaning of certain medical terminologies might be hindered. This might have a detrimental effect on their clinical practice in the future which may be directly related to less than optimal patient care.

## Key Words

Latin, Greek; Terminology; Medicine; Medical Education; Clinical Practice

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## Introduction

The origin of medical terminology is a rich area of research which encourages the field of Medical Science to interact with that of Translation Studies, a collaborative opportunity which has not been fully explored or its potential reconnoitred within the world of academia. The language of medicine offers intriguing challenges and opportunities both to medical historians and to linguists. The majority of medical terms used today throughout Europe, and even beyond, are of Greek or Latin origin. Clinical terminology tends to derive from Greek (*dermatitis*, *laryngotomy*, *gastroscopy*) while anatomical vocabulary is often rooted in the Latin language (*dorsum*, *medialis*, *ventriculus*).

## A Brief History of Medical Language

The Greeks founded rational medicine and dominated the field until the beginning of the 18<sup>th</sup> Century. It is thus estimated that three quarters of medical terminology derives from the Greek language. Hippocratic writings of the 4<sup>th</sup> and 5<sup>th</sup>

centuries BC form the foundation of modern medicine. This collection of Greek medical works, which indicate numerous concepts and terminologies pertaining to the field of medicine, marked the beginning of the Greek influence in the language of Western medicine. The influence of this period is still evident in the medical terminology used in today's practice. In particular, the names of numerous diseases and symptoms derive from Greek. Examples include *arthritis* (from the Greek *arthron* [meaning joint] and *-itis* [meaning inflammatory disease]), *dermatitis* (from the Greek *derma* [meaning skin] and *-itis* [meaning inflammatory disease]), and *pneumoconiosis* (from the Greek *pneumōn* [meaning lung], *konis* [meaning dust], and *-osis* [meaning disease]), to name a few.

In the 1<sup>st</sup> Century AD, the Roman encyclopaedist Aulus Cornelius Celsus (c.25 BC – c.50 AD) wrote *De Medicina*, an overview of medicine based on numerous Greek sources. Realising that there was no Latin equivalent for the majority of Greek

medical terminologies, Celsus implemented strategies which would allow the core medical aspects to reach those versed in Latin. He borrowed words directly from Greek, such as *pyloros* (now *pylorus*). In addition, he adapted Greek terms in order to make them suit the Latin alphabet and pronunciation. For example, the Greek word *krānion* (meaning *skull*) became *crānium*.

During the Middle Ages, medical works were translated into Arabic and Arabic terms such as *carania* (meaning *cornea*), *al-batan* (meaning *abdomen*), *bu'bo* (meaning *pupil*) and *ein* (meaning *eye*), were encouraged to enter the medical language of the Western world. Yet, the Renaissance period saw a decline in the widespread use of Greek and, subsequently, existing medical works were translated into Latin while new texts were written in this language. This signalled the beginning of the Latin influence in medical terminology.

The Romans continued to study the field of medical science and encouraged Latin terminologies to enter its vocabulary. In addition, Latin was considered the language of science, and therefore medicine, until the start of the 19<sup>th</sup> Century. This led to numerous texts, including Andreas Vesalius's anatomical work *De humani corporis fabrica* (1543), appearing in Latin. From the beginning of the 19<sup>th</sup> century, national languages, including English, French, German and Italian, gained prominence which resulted in the decline of Latin. Each language developed its own medical terminology but, since the majority of terms derived from Latin, there were commonalities which are still apparent today. Due to the constant advances in medicine, it is essential to create and implement newer medical terminologies. Words are needed to denote new diseases, conditions, instruments and technologies. Following the decline of Latin, the medical community now tends to implement terms of Greek origin since this language allows the composition of new words to an easier extent than Latin (e.g., *pneumectomy* and *otoscopy*). Furthermore, Greek prefixes and suffixes including *-itis* and *hyper-* were employed, leading to the formation of terms such as *appendicitis* and *hypertension*.

Today, English is seen as 'the language of medicine'. Most influential medical journals use the medium of English and international conferences tend to be held in English. As innovative medical concepts are developed and medical technology advances, English words enter the medical terminology. For example, the terms *screening* and *scanning*. Medical inventions will continue to emerge and it is possible that scholars will employ words which are common in the English language rather than rely on terms of

Greek or Latin origin. Nevertheless, the Greek and Latin roots of a significant number of medical terminologies which are common in today's practice are visible and cannot be easily ignored.

The Doctors Academy International Medical Summer School is a global educational event which attracts medical students of all years from universities throughout the world. The School covers all specialities and comprises of over 80 lectures and 10 workshops during the week. Since it is the only event of its kind in the world, it provided a unique platform for this study and offered the opportunity to assess the awareness not only of medical students studying in the United Kingdom but also of those studying in various countries worldwide. A total of 218 students attended the 2015 Summer School, enabling the study to be conducted amongst a large audience and facilitating a wide, international study.

This study aimed to evaluate the extent to which medical students are aware of the origin of the medical terminologies which are used in everyday practice today. The results will enable researchers to determine if there is a correlation between a medical student's knowledge of Greek or Latin and his or her understanding of medical terminologies.

### Methodology

A survey was conducted on 218 medical students from 28 countries worldwide during the 2015 Doctors Academy International Medical Summer School which was held at the University of Manchester, United Kingdom, between 27<sup>th</sup> - 31<sup>st</sup> July 2015.

The 218 participants were seated in a lecture theatre with sufficient space between each individual to ensure that there was no conferring. Each participant was given an exercise sheet (see *Appendix A*) and asked to complete it alone and in silence within the stipulated time of twenty minutes. Invigilators were present for the duration of the study to ensure that the participants did not engage in discussion. After the twenty minutes had passed, the papers were collected by the invigilators and the data was later analysed.

The paper consisted of 60 questions which were divided into four sections. The first section, comprising of 10 questions (see *Appendix B*), was out of a total of 10 while the second section, comprising of 14 questions (see *Appendix C*), was out of a total of 21. The third section, comprising of five questions (see *Appendix D*), was out of a total of eight and the fourth section, comprising of 11 questions (see *Appendix E*), was out of a total of 21.



A total of 218 papers were collected, marked, scored, and analysed.

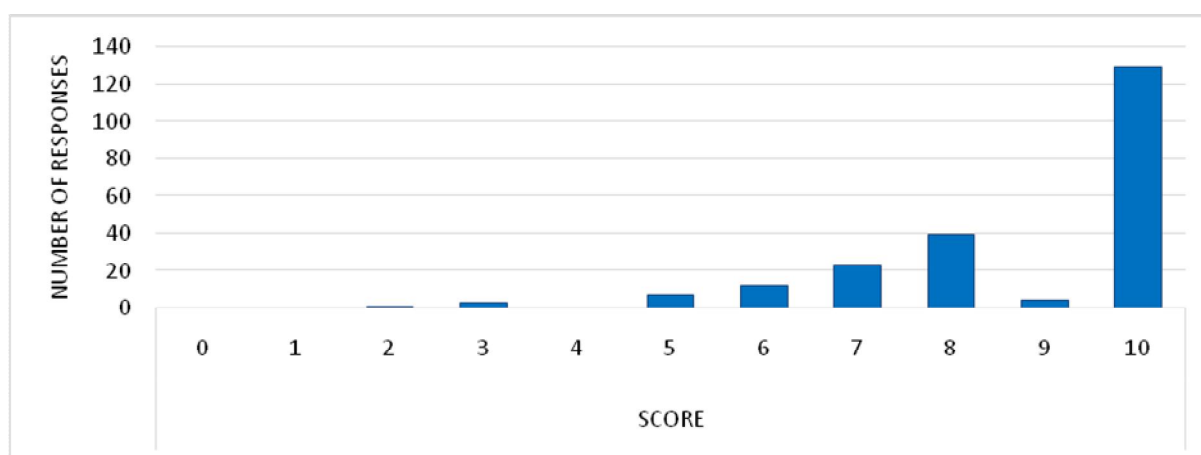
## Results

### Section 1

The first section provided a list of ten prefixes and suffixes in Greek or Latin which form part of numerous common medical terminologies. The

meaning of each prefix and suffix was also given in English. Participants were asked to match the Greek or Latin prefixes and suffixes with their English meaning.

The graph indicates that the majority of participants (129 in total) attained the maximum score of 10. The other participants also scored highly, with two being the lowest score achieved by only one individual.

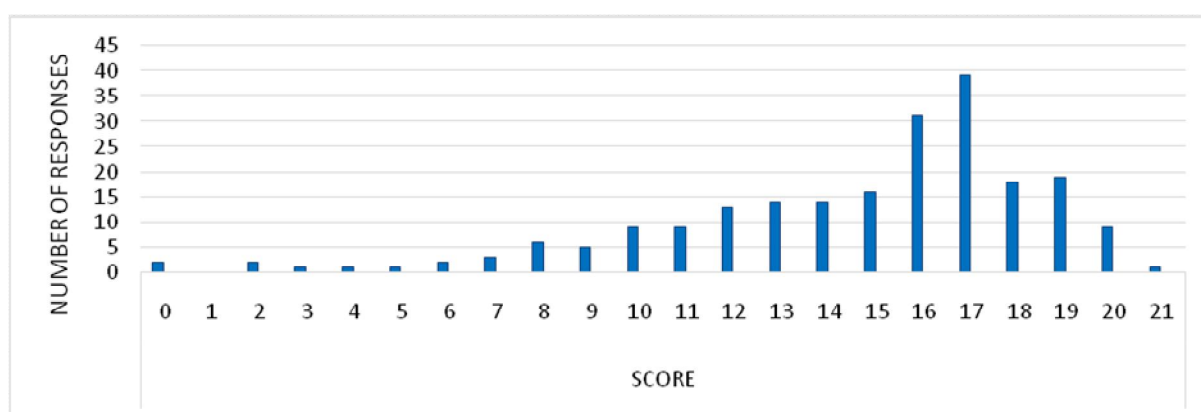


**Figures 1:** The graph shows how the participants scored in Section 1 which asked 'Match the following Greek and Latin prefixes and suffixes with their meaning in English. Draw lines to link the answers.'

### Section 2

In order to complete the second question, participants were given 14 prefixes and suffixes which are either Greek or Latin and form a large number of common medical terminologies. They were required to explain the meaning of the Greek

or Latin term, as well as provide an example of each prefix or suffix used as part of a word relating to the field of medicine. For the sake of clarification, an example was provided. In addition, the meaning of certain prefixes and suffixes was offered in order to aid those whose first language was not English.

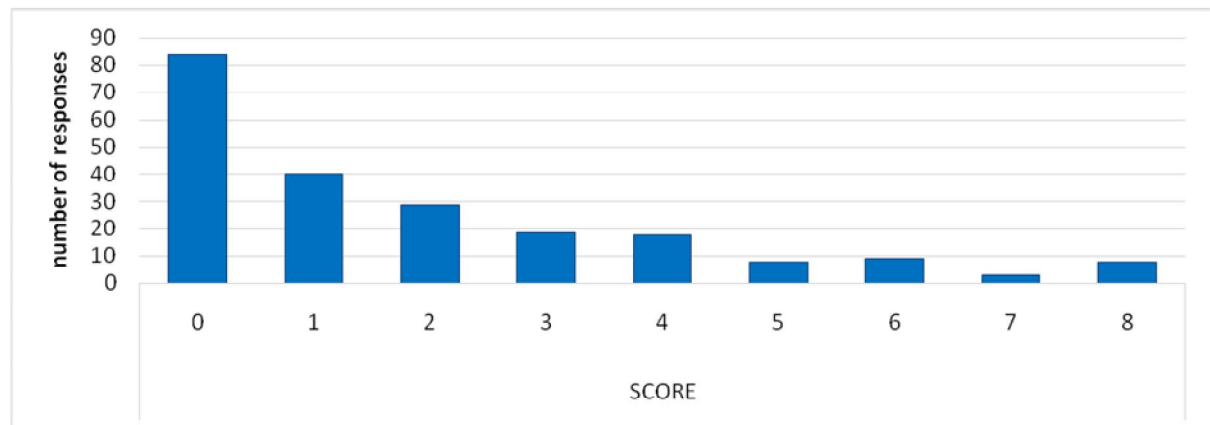


**Figures 2:** The graph indicates the way in which the participants scored in Section 2 which asked 'Below you have a list of prefixes and suffixes commonly used in medicine. Please explain their meaning and give an example for each one.'

### Section 3

Participants were presented with five medical terms in English and asked to state the Greek or Latin word from which they derive. They were also required to give an example of a common medical term which uses the Greek or Latin derivative. Two answers were completed in order to provide the participants with examples.

The graph indicates that the greatest number of participants (84 in total) scored 0. The number of participants attaining a high score remained low: eight out of a total of 218 participants obtained the maximum score of eight and three participants gained seven.

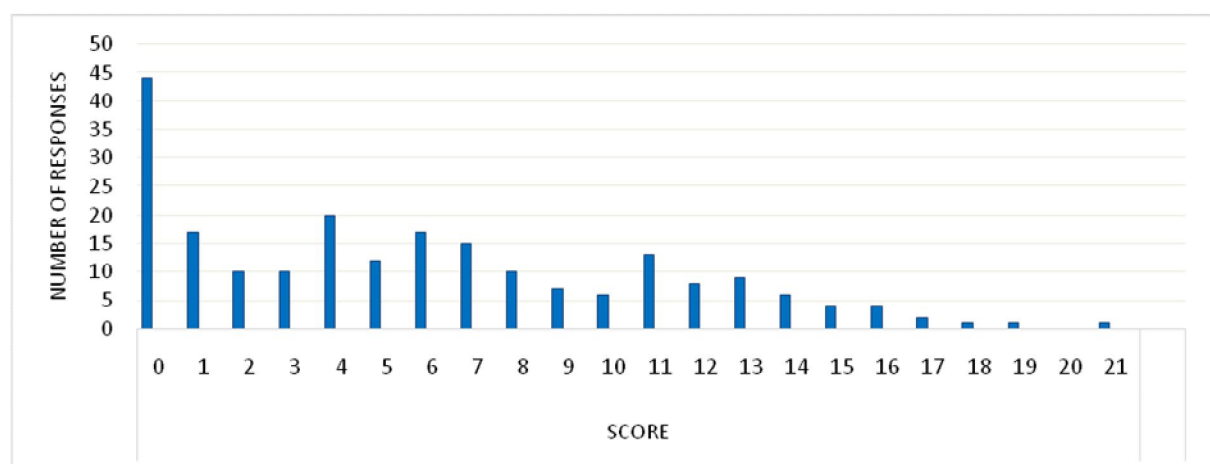


**Figures 3:** The graph reveals how each participant scored in Section 3 which asked 'Below you have a list of English medical terms. Please state the Latin or Greek word from which they derive.'

### Section 4

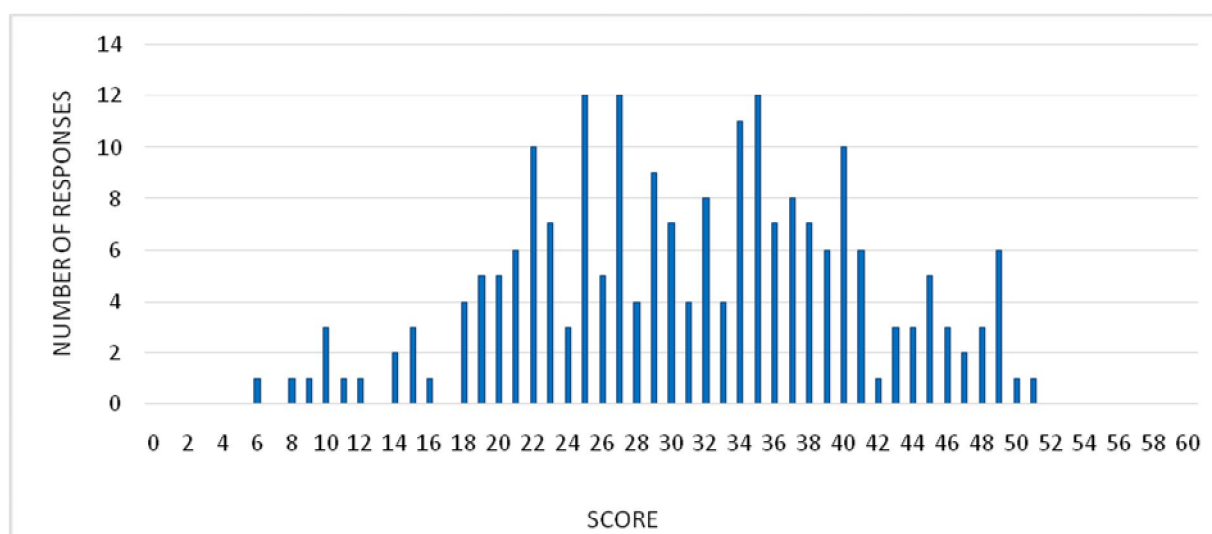
The final question provided explanations of 11 medical terminologies and asked participants to state the Latin or Greek word from which these terms derive. Participants were also required to give an example of each term employed in an anatomical context.

The graph demonstrates that one of the 218 participants scored the maximum score of 21 while the greatest number of participants (44 in total) scored 0. A large number of participants obtained a low score, with 20 scoring four and 17 scoring six.



**Figures 4:** The graph illustrates the way in which each participant scored in Section 4 which asked 'Below you have explanations of words. Please state the Latin or Greek word from which they derive and give an example.'

## Overall Score



**Figures 5:** The graph indicates the overall score of individual participants with the particular score correlated to the number of responses.

The graph reveals the overall score achieved by each participant with the particular score correlated to the number of responses. The maximum score of 60 was not attained by any participant; the highest score was 51 which was obtained by one participant. The lowest score achieved was six. The majority of participants obtained a total score between 18 and 41 which indicates that the results were mixed.

## Discussion

The results suggest that medical students do not have adequate understanding of the Greek or Latin origin of common medical terminologies. That the overall scores were relatively low and the maximum score of 60 was not obtained by any participant support this assertion.

While the majority of participants achieved a maximum score of 10 in the first section, it is vital to remember that both the Greek or Latin forms and the English equivalents were offered. It could therefore be argued that the medical students were able to deduce the Greek or Latin terminologies when all of the required information was presented. This corresponds to the 'remembering' level of Bloom's Taxonomy of Learning Domains (1956; 2001) where the learner is encouraged to recognise and retrieve terms, concepts or facts without necessarily understanding the meaning. The first section in this survey tested the participants' basic recall of facts and, therefore, the tendency to score highly does not indicate that the participants were truly aware of the origin of the medical terminologies.

In order to complete the second section, participants were given Greek or Latin terminologies, as well as the English meaning of half of the words. The Greek and Latin derivatives which formed the question are recognisable to those working in the field of medical science. For example, the Greek derivative '-iatrics' was provided and resulting terms, such as 'paediatrics' and 'geriatrics', are frequently used today. This question resembles the second level of Bloom's Taxonomy: 'understanding'. A learner at this level is able to comprehend the meaning of a term, concept or fact and offer his or her own example. The question assessed the extent to which the participants recognised the Greek and Latin influence in medical vocabulary. That many participants scored relatively highly indicates that there is some recognition of this.

The third and fourth sections contained fewer completed answers which meant that participants were encouraged to generate more responses independently. It could be suggested that this was a primary reason for a large number of participants achieving a low mark in both of these sections. Furthermore, sections three and four required participants to give the Greek or Latin terms, as opposed to sections one and two which demanded the English words. These two sections reflect the 'applying' phase of Bloom's Taxonomy since participants were invited to utilise existing knowledge, namely Greek or Latin terminologies that are frequently employed in current practice, in a new situation. That many students struggled to offer the correct answers could reflect two

indications: medical students show little awareness of the Greek and Latin origin of common medical terminologies or the knowledge that medical students possess of the Greek and Latin origin of common medical terminologies is not harnessed sufficiently to allow them to apply it within new situations.

It is vital to consider that the 218 medical students who participated in this survey are of different nationalities and have various native languages. Since delegates of the International Medical Summer School are not required to possess an indicated standard of English language proficiency in order to attend the event, it is supposed that each participant's competence in English differed. While the students would have possessed at least a minimum standard of English language proficiency, the exact level is unknown. It is probable that some participants would have possessed limited skills in the English language whilst others would have achieved a high standard of proficiency. This disparity will have impacted the results of the survey since the participants would have been influenced by their knowledge of the English language. In order to illustrate this in a clear manner, we will take section three as an example. Student A, whose native language is Russian and who did not possess a high standard of English language proficiency, did not understand the medical terminologies written in English and presented in this question. His limited knowledge of the English language prevented him from completing the question and he scored 0. This does not, however, imply that he does not know the Greek or Latin derivative of the English word. He is unable to interact in English but he would have been able to respond correctly if the terminologies had been offered in his native language of Russian.

Furthermore, it is anticipated that some participants with a limited proficiency in the English language would have struggled to understand the questions. This may have prompted incorrect or ill-informed answers. In addition, that participants were required to complete the paper within a stipulated time would have prevented some from offering the correct answers. Indeed, it is expected that those with a minimum standard of English language proficiency will be unable to engage with the question as rapidly as those whose native language is English.

The native language of certain participants was Greek. These students would have approached the paper from a different perspective and the challenges faced would have differed from those tackled by native speakers of English, for example. While these participants may have understood the

Greek derivatives of the medical terminologies with relative ease, it is possible that they would have struggled to express the answer in English for the reasons highlighted in the previous paragraph.

As a final point of consideration, it is important to note that the participants' level of knowledge of Greek and/or Latin was varied. Certain countries include Greek and Latin in the national curriculum and, as such, children learn these languages from a young age. For example, in Italy, Latin is compulsory for students who attend the *Liceo scientifico* and the *Liceo classico* while Ancient Greek is also compulsory for those attending the *Liceo classico*. To this end, some participants would have been in an informed position. Moreover, Romance languages such as French and Italian directly descend from Vulgar Latin, a form of non-classical Latin. Participants whose native language was a Romance language, as well as those who possessed a high level of proficiency in a Romance language, would arguably have responded to the questions in a different manner to those whose mother tongue was a Germanic language.

### Conclusion

The language of medicine is a rich and intriguing area of study for both linguists and medical doctors. Exploring the flow of terminologies from one vernacular to another proves fascinating for linguists while an appreciation of the history and origin of words used in medical practice will offer a new dimension to the professional knowledge, language, and practice of doctors. Awareness of the origin of medical terminologies boasts a valuable academic significance. In addition to this, a perspicacity of the history of medical language will encourage medical students and doctors to conceptualise anatomical terms, pathologies, and treatments in a less arduous manner. This will prove vital to the development of a clinician's career, as well as help him or her to contribute to medical patois, all of which will eventually benefit and enhance patient care. It can therefore be suggested that prospective medical students should consider learning the fundamental concepts of the Greek and Latin origin of medical terminologies before commencing their medical studies.

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## Appendices

### Appendix A: Exercise Sheet

#### INTERNATIONAL STUDY OF MEDICAL STUDENTS/JUNIOR DOCTORS EVOLUTION AND HISTORY OF MEDICAL TERMINOLOGIES

1. Match the following Greek and Latin prefixes and suffixes with their meaning in English. Draw lines to link the answers.

- |            |                      |
|------------|----------------------|
| a) -algia  | 1) reconstruction    |
| b) -ectomy | 2) rotten            |
| c) -plasty | 3) wound             |
| d) trauma  | 4) excision          |
| e) onco-   | 5) pain/inflammation |
| f) septi-  | 6) swelling          |
| g) -tomy   | 7) bad, faulty       |
| h) ectop-  | 8) displaced         |
| i) dys-    | 9) incision          |
| j) gangli- | 10) tumour           |

2. Below you have a list of prefixes and suffixes commonly used in medicine. Please explain their meaning and give an example for each one. The first one has been completed for you as an example

LATIN/GREEK WORD	MEANING	EXAMPLE
- IATR(O)	Doctor	Iatrogenic
-IATRICS		
-OSIS	Condition or disease	
SEPTI-		
TUBER-	Swelling	
THROMB (O)-,		
-ITIS		
ASTHEN-	Weakness	
PLEGIA-	Paralyse	
-ECTOMY		
-TOMY	Incision (operation by cutting)	
-STOMY		
-OPSY	Examination	
-SCOPY		
VOLV-	Rotate	

3. Below you have a list of English medical terms. Please state the Latin or Greek word from which they derive?

ENGLISH TERM	LATIN OR GREEK DERIVATIVE	EXAMPLE
Drug		
Poison		
Pus		
Grease	SEB(O)-	
Shield		Thyroid gland

4. Below you have explanations of words. Please state the Latin or Greek word from which they derive and give an example. The first one has been completed for you as an example.

MEANING	LATIN OR GREEK DERIVATIVE	ANATOMICAL EXAMPLE
<b>Rock</b>	<b>Petrous</b>	<b>Petrous bone in skull</b>
Shell-like (located within head)		
Resembling spider's web (located within skull)		
Short		
Deep		
Drowsiness (artery in the neck)		
Wandering, straying (cranial nerve)		
Body		
Hard protector (located within brain)		
Receiving chamber		
Groove or trench		
Yellow	Flavus	

### Appendix B: Section 1 of Exercise Sheet

1. Match the following Greek and Latin prefixes and suffixes with their meaning in English. Draw lines to link the answers.

- k) -algia
- l) -ectomy
- m) -plasty
- n) trauma
- o) onco-
- p) septi-
- q) -tomy
- r) ectop-
- s) dys-
- t) gangli-

- 1) reconstruction
- 2) rotten
- 3) wound
- 4) excision
- 5) pain/inflammation
- 6) swelling
- 7) bad, faulty
- 8) displaced
- 9) incision
- 10) tumour

### Appendix C: Section 2 of Exercise Sheet

2. Below you have a list of prefixes and suffixes commonly used in medicine. Please explain their meaning and give an example for each one. The first one has been completed for you as an example.

LATIN/GREEK WORD	MEANING	EXAMPLE
- IATR(O)	Doctor	Iatrogenic
-IATRICS		
-OSIS	Condition or disease	
SEPTI-		
TUBER-	Swelling	
THROMB (O)-,		
-ITIS		
ASTHEN-	Weakness	
PLEGIA-	Paralyse	
-ECTOMY		
-TOMY	Incision (operation by cutting)	
-STOMY		
-OPSY	Examination	
-SCOPY		
VOLV-	Rotate	

### Appendix D: Section 3 of Exercise Sheet

3. Below you have a list of English medical terms. Please state the Latin or Greek word from which they derive?

ENGLISH TERM	LATIN OR GREEK DERIVATIVE	EXAMPLE
Drug		
Poison		
Pus		
Grease	SEB(O)-	
Shield		Thyroid gland

**Appendix E: Section 4 of Exercise Sheet**

4. Below you have explanations of words. Please state the Latin or Greek word from which they derive and give an example. The first one has been completed for you as an example.

MEANING	LATIN OR GREEK DERIVATIVE	ANATOMICAL EXAMPLE
Rock	Petrous	Petrous bone in skull
Shell-like (located within head)		
Resembling spider's web (located within skull)		
Short		
Deep		
Drowsiness (artery in the neck)		
Wandering, straying (cranial nerve)		
Body		
Hard protector (located within brain)		
Receiving chamber		
Groove or trench		
Yellow	Flavus	



# Proceedings from the first International Conference on RASopathies in Asia: Advances in RASopathies and Neurofibromatoses and in Identification of New Therapeutic Targets

27<sup>th</sup> – 29<sup>th</sup> November 2017

Crown Plaza Hotel, Kochi (Cochin), Kerala, India

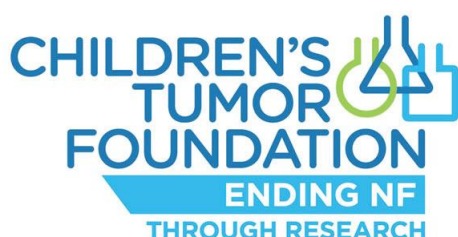


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PARK

PARC  
Genetec  
CYMRU



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University of Wales  
Trinity Saint David

**Introductory Message from Professor Meena Upadhyaya OBE, Conference Organiser**



I am pleased to report about the first RASopathy meeting that was held in Asia and we were honoured to host many prestigious speakers and attendees from more than 20 countries around the world.

I first visited Kerala, often dubbed as "God's own Country" more than 10 years ago and instantly fell in love with this place as I was driven through the lush green tea plantation of Munnar, a very popular hill station in Kerala. The backwaters of Kerala also offered amazing experiences, with Thakkedy, India's largest wildlife sanctuary, being a dream destination for all lovers of nature.

The idea of organizing an international conference arose at that time despite not having either any academic connections with, or knowing the language or culture of Kerala. So it has taken a decade to come to fruition and it was at last year's NF European meeting in Padua that I asked several colleagues whether they would be interested in attending a RASopathy meeting in Kerala, and, to my great surprise and delight, I received a very enthusiastic response and now have done it!

I must express my gratitude to my co-organisers, Ashok Pillai, Gareth Evans, Joshi George and Stuart Enoch for their unfailing support. We must also thank our many generous sponsors: Astra Zeneca, Cardiff University, the Children's Tumour Foundation, University of Wales Trinity Saint David, the Wales Gene Park, Neuro Foundation, Medgenome, Schiller India, Axis Health Biomedicals and The Doctors Academy Group. I must also give special thanks to Angela Burgess and I am grateful to Nigel Burgess, Narendra V, Prasanth AS, Sheela Nam-poothiri and IC Verma for their support. Finally, I thank Crowne Plaza, Kochi for hosting this event.

On the first evening, we had a Gala Dinner organized at Crowne Plaza, where we were entertained with classical Indian music and Bollywood dancers, and many faculty had the opportunity to participate in the dance activities! The following day, they were taken to Cherai beach and they partook in the Kerala barbecue on the resort's private beach and were also entertained with Kathakali dancers.

Now back to the conference: in the UK it is estimated some 50,000 people may be affected by RASopathies. Over the past 10 years, many significant advances have been made in our ability to discover, validate and translate our laboratory-based research findings into practical clinical applications. The many sophisticated animal models being developed are also facilitating the evaluation of rational targeted treatments. So, I am certain we can now start to envisage a future where effective RASopathy treatments will soon become available.

The organizing committee endeavored to ensure a comprehensive programme of interest and relevance to all healthcare workers: clinicians, scientists, genetic counselors, nurses as well as patients. Hence, we equally focused on both bench-to-bedside and a bedside-to-bench strategies.

I sincerely hope that this meeting proved to be pivotal in helping to facilitate exchanges of ideas, future collaborations, the promotion of good clinical and scientific practice, as well as sharing innovative and emerging trends.

I also hope that the delegates had the chance to sample the natural beauty, the delicious cuisine and the hospitality of Kerala during their stay.

*meena upadhyaya*

## DAY 1: CLINICAL ASPECTS OF NF1, NF2 AND SWANNOMATOSIS

### Professor Katherine Rauen, California, USA



Katherine (Kate) Rauen, MD, PhD is a Professor in the Department of Pediatrics, Division of Genomic Medicine at the UC Davis where she currently serves as the Chief of Genomic Medicine and holds the Albert Holmes Rowe Endowed Chair in Human Genetics. She received a MS in Human Physiology and a PhD in Genetics from UC Davis doing research on gene dosage compensation and genetic evolution. She obtained her MD at UC Irvine where she also did research in cancer genetics. Dr. Rauen did her residency training in Pediatrics and fellowship in Medical Genetics at UC San Francisco.

Dr. Rauen is internationally known for her pioneering work in the early application of microarray technology in clinical genetics and as a leader and major contributor to the understanding of the "RASopathies", the Ras/MAPK pathway genetics syndromes. Her research program involves the clinical and basic science study of cancer syndromes with effort to identify underlying genetic abnormalities affecting common developmental and cancer pathways. Dr. Rauen led the research team, including the CFC International Family Support Group that discovered the genetic cause of cardio-facio-cutaneous syndrome and independently identified the genetic cause of Costello syndrome.

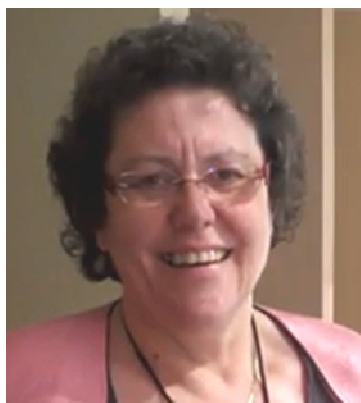
Dr. Rauen is committed to academic medicine, medical education, and advancing best practices for patients with RASopathies. She has successfully obtained both intramural and extramural funding for her research activities, and currently holds a 5-year NIH grant studying skeletal myogenesis in Costello syndrome and CFC. She is the innovator of the world-renowned NF/Ras Pathway Clinic which she initiated in 2007 and this clinic has now been emulated around the globe. She serves on the medical advisory board of CFC International, is a Co-Director for the Costello Syndrome Family Network, and serves on the advisory boards for RASopathies Network USA and Global Genes.

Dr. Rauen was recently awarded the Presidential Early Career Award for Scientists and Engineers (PECASE) on her work for CFC and Costello syndrome. This Award is the highest honor bestowed by the United States Government on science and engineering professionals in the early stages of their independent research careers. This Presidential Award is awarded for innovative and far-reaching developments in science and technology, in an effort to increase awareness of careers in science and engineering, give recognition to the scientific missions of participating agencies, enhance connections between fundamental research and national goals, and highlight the importance of science and technology for the nation's future. Additionally in June 2014, Dr. Rauen won an International Advocacy Award, the "Global Genes RARE Champion of Hope in Science".

### RASopathies Overview

The RASopathies are a group of clinically related developmental disorders which are caused by germline mutations in genes that encode components, or regulators of the Ras/mitogen activated protein kinase (MAPK) pathway. As a group, the RASopathies are one of the largest groups of malformation syndromes known, affecting approximately 1:1,000 individuals. The Ras/MAPK pathway plays an essential role in the regulation of the cell cycle, differentiation, growth and cell senescence, all of which are critical to normal development. As a result, Ras/MAPK pathway dysregulation has been shown to have profound deleterious effects on both embryonic and later stages of development. Because the underlying molecular mechanism for these syndromes is dysregulation of the Ras/MAPK pathway, the RASopathies exhibit numerous overlapping phenotypic features, including reduced growth, characteristic facial features, cardiac defects, cutaneous abnormalities, neurocognitive delay and a predisposition to neoplasia, both benign and malignant.

**Dr Susan Huson, Manchester, UK**



Sue trained in medicine in Edinburgh and after general training in adult medicine and neurology, moved to a research post Professors Peter Harper and Alastair Compston in Cardiff. She started the post as a would-be neurologist and switched to a clinical genetics career mid-way. Her Welsh population based study of neurofibromatosis type one (NF1) and gene mapping studies led to the award of MD with gold medal and distinction. She then trained in clinical genetics at the Kennedy Galton Centre, London. As a consultant, first in Oxford and then in Manchester, she developed her interest and expertise in the diagnosis and management of all forms of neurofibromatosis. From April 2009 – April 2017 she led the nationally commissioned service for complex NF1 in the north of England. Sue has co-edited two books, numerous book chapters and research papers on neurofibromatosis.

**Neurofibromatosis type one (NF1): diagnosis, natural history and management Dr Sue Huson, Consultant Clinical Geneticist (retired), Manchester**

Alongside Noonan syndrome, NF1 is one of the most common Rasopathies with a birth incidence of approximately 1/2500. It results from mutations in the NF1 gene on chromosome 17. Inheritance is autosomal dominant and 50% of cases are new mutations. The diagnosis is made using the clinical criteria developed at the 1987 NIH consensus conference. Both Legius syndrome and constitutional mismatch repair deficiency syndrome can be misdiagnosed as NF1 using current criteria. Furthermore, specific genotype-phenotype correlations are emerging. Review of the diagnostic criteria at a CTF sponsored workshop is planned for 2018. The major features of NF1 are café au lait patches +/- skinfold freckling, iris Lisch nodules and neurofibromas. Of these only the neurofibromas are associated with significant morbidity. There are three main types of neurofibroma the cutaneous, the nodular and plexiform. Most people with NF1 have a varying number of cutaneous neurofibromas – these are not associated with malignant change but are the major cause of cosmetic morbidity for NF1 adults. Nodular neurofibromas are those on the major peripheral nerves and usually appear from around 10 years of age. Only a subset of patients develop them. Studies have shown that patients with multiple nodular lesions have multiple internal lesions putting them at increased risk of MPNST. Plexiform neurofibromas occur in about 30% of patients and vary from diffuse superficial lesions to those affecting a whole-body part.

People with NF1 are at risk of many complications which can affect almost any body system. In childhood the major issue is learning and behavior problems with 40-50% having associated ADHD and 25% ASD. Large population studies have shown that people with NF1 have a 59.6% lifelong risk, the highest risk being of MPNST and CNS tumours. However other tumours are associated with women with NF1 having an increased risk of NF1 to age of 50 years.

People with NF1 find the uncertainty and unpredictability of their condition a challenge. This aspect also makes planning a care pathway for NF1 difficult. Even patients with apparently mild disease remain at risk of NF1 related tumours as adults. In England the NHS has funded two supraregional centres with multidisciplinary teams to manage the complex NF1 patients. Children are followed by local paediatricians. Many adults with NF1 have no formal review. The Neuro foundation are gradually developing a nationwide network of specialist advisors so everyone with NF1 has access to someone with expert knowledge.



### **Dr Ratna Puri, Delhi, India**



Dr Ratna Dua Puri completed her MD in Pediatrics at the Armed Forces Medical College and DM in Medical Genetics from SGPGI, Lucknow. Her current appointment is Professor and Chairperson, Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi. Dr Puri is also President of the Society of Fetal Medicine, a Founder Member of the Society of Indian Academy of Medical Genetics and Past secretary, Genetic chapter of the Indian Academy of Pediatrics

Dr Puri's interests include diagnosis and management of rare disorders, specifically within the area of dysmorphology, malformations, fetal evaluation for etiology, lysosomal storage disorders and education in the evolving field of genetics

Dr Puri's salient achievements are:

1. Dharam Vira Award of Excellence in recognition of meritorious service rendered to the Sir Ganga Ram Hospital during the year 2010
2. Member of the National Institute of Health, USA, Undiagnosed Diseases Network, an initiative on rare and undiagnosed disorders.
3. "Young Investigators Award" at the International Congress of Inborn Errors of Metabolism held in Tokyo, Japan from 12-16th September 2006 for the paper "Spectrum of Urea Cycle Disorders in the Indian population and prenatal diagnosis.
4. Invited as the representative from India for deliberations at the Joint World Health Organization & March of Dimes Meeting on "Management of Birth Defects and Hemoglobin Disorders" in Geneva in May 2006.
5. Member of the DHR – ICMR, Task Force on Birth Defect Registry in India and Lysosomal Storage Disorders task force, an initiative of the Indian Council of Medical Research as well as a member of the project screening committee of the Department of Health Research, Ministry of Health, Government of India.

### **RASopathies: The Indian Experience**

The RASopathies are a specific group of genetic syndromes that occur as a result of germline mutations in genes encoding proteins of the Ras-mitogen-activated protein kinase (RAS-MAPK) pathway. These developmental disorders include Neurofibromatosis type 1 (NF1), the first RASopathy identified, followed by Noonan syndrome (NS), and a host of others including Noonan syndrome with multiple lentigines (NSML), capillary malformation-arteriovenous malformation syndrome (CM-AVM), Costello syndrome (CS), cardio-facio-cutaneous syndrome (CFC) and Legius syndrome. This is one of the largest group of malformation syndromes with an estimated incidence of about 1 in 1000 persons.

In my talk I will be discussing the spectrum of patients seen at our clinic at a referral genetic centre, mostly diagnosed to have NF1 and Noonan syndrome, over a period of 8 years and detailing a few interesting cases. The age of presentation of patients with Noonan syndrome varied from 3 months to 22 years and one fetus was clinically suspected after termination of the pregnancy at 18 weeks gestation. Short stature was a consistent feature in all patients. The characteristic facial dysmorphism was present in 88% cases. The patients with cardio-facio-cutaneous syndrome had a broader, coarse looking face with sparse, thick, curly wooly hair. Cardiac disease was present in 83% cases. Pulmonary valvular stenosis was the commonest followed by hypertrophic cardiomyopathy and atrial septal defects. One girl was a mosaic Turner syndrome with mutations in SOS1 gene implicated in Noonan syndrome. Another child presented with features of NF1 and Noonan syndrome with a truncating mutation in NF1 gene. Another child presented at 3 months of age with JMML syndrome and was confirmed to have a mutation in PTPN11 gene. In this cohort antenatal data of three patients was available and this included increased nuchal fold thickness, pulmonary stenosis, polyhydramnios and pulmonary stenosis. An 8 months old child presented with pulmonary stenosis and atrial septal defect, mild developmental delay and coarse facies had a pathogenic mutation in the SHOC2 gene.

In a recent publication in a cohort of 17 Indian patients, PTPN11 mutation accounted for 64.7% of cases with clinical features of Noonan syndrome. Majority of the mutations were in exon 3 and exon 13 of PTPN11 gene, making them possible hotspots in Indian population. In a South Indian population, a mitochondrial DNA haplogroup "R" is reported to be associated with Noonan Syndrome. Noonan syndrome with craniosynostosis with germline mutations in the KRAS gene is reported in a young infant of Indian origin with Noonan syndrome.

### **Professor Ashok Pillai, Kochi, India**

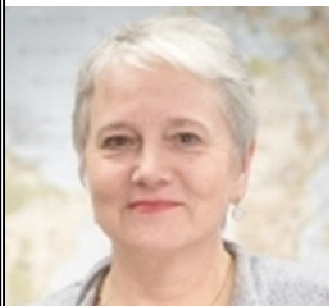


Dr. Ashok Pillai is a professor of neurosurgery and neuroscience associated with Amrita Institute of Medical Sciences, Kochi. After completing his initial college education in the neurosciences, medical college and surgical training in the United States, he migrated back to India to join AIMS, Kochi in 1999. After completion of his neurosurgical training, he pursued further advanced training in Canada and the United States in the field of epilepsy surgery and other areas of functional neurosurgery. In the field of neurooncology, Dr. Ashok Pillai has maintained a dedicated clinical and research interest in familial tumor syndromes - namely von Hippel Lindau and the neurofibromatosis. Presently, Dr. Ashok Pillai heads the epilepsy surgery program, neurooncology program (dealing with adult and paediatric brain tumors), and the peripheral neurosurgery program at AIMS, Kochi. He excels in stereo-

tactic neurosurgery and is a pioneer in the upcoming field of robotic neurosurgery. He also has a dedicated interest in pediatric neurosurgery.

### **RASopathies: Indian experience**

### **Professor Ludwine Messiaen, Birmingham, USA**



Professor Ludwine Messiaen holds a PhD in Cancer Biology from the University Ghent, Belgium, where she was on faculty until 2003. In 2003, she joined the University of Alabama in Birmingham as a Professor in Genetics and Director of the Medical Genomics Laboratory, specializing in clinical testing for all rasopathies, with focus on all neurofibromatoses.

She is interested to fully explore the spectrum of NF1 mutations, including mutations not readily identified by DNA-based analysis of the coding regions (e.g. deep-intronic splice mutations or retrotransposon-mediated mutations).

Her group described the presence of 2 NF1 hits in the melanocytes of CALMs, but not in the keratinocytes or fibroblasts.

Professor Messiaen explores NF1 genotype-phenotype correlations using several complementary approaches. She developed and curates a patient database with de-identified genotypes and phenotypes of over 8,500 unrelated NF1-mutation-positive individuals.

Her lab actively engages in the identification of novel genes contributing to the neurofibromatoses. This includes involvement in the identification of Legius syndrome. After SPRED1 gene discovery, she substantially contributed to the quick delineation of the full breath of phenotypes associated with this novel rare disorder. Furthermore, her research on a well-characterized patient cohort recently led to the identification of LZTR1 as a novel major schwannomatosis-predisposing gene.

### **NF1 mutational spectrum and quest for genotype phenotype**

Clinical variability, both inter- and intrafamilial, has been widely reported in the past two decades. The factors contributing to the phenotypic variability include: i/ age-dependency of some of the NF1 features; ii/ the timing, cell-of-origin and number of second hits in specific cells; iii/ post-zygotic mosaicism for the first NF1 hit in mosaic individuals; iv/ the enormous NF1 allelic heterogeneity with over 3000 different NF1 mutations

identified to date in our lab; v/ occasional presence of two different NF1 pathogenic variants within a family or the occurrence of two independent mutations (one in the NF1 gene and the other in a different gene) in an individual; vi/ modifying genes [89] and vii/ environmental factors (e.g. number of pregnancies).

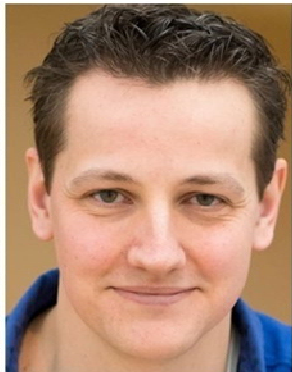
Only few clinically relevant genotype-phenotype correlations have been so far reported: first, individuals with a constitutional NF1 microdeletion more frequently present with a large number of neurofibromas at young age, dysmorphic facial features and developmental delay. Second, individuals with the single amino acid deletion p.Met992del present with a milder pigmentary phenotype without externally visible cutaneous or plexiform neurofibromas. Third, missense mutations affecting amino acid 1809 equally do not develop external plexiform or cutaneous neurofibromas, or symptomatic OPG, but more frequently have Noonan-like features, including pulmonic stenosis. p.Met992del as well as Arg1809 reside outside of the GAP-related domain.

We now identified a cluster of missense mutations affecting amino acids 844-848, residing in the Cysteine-Serine Rich Domain. Individuals carrying a constitutional missense mutation affecting these residues have a high prevalence of a severe phenotype, including plexiform and symptomatic spinal neurofibromas, symptomatic optic pathway gliomas, other malignant neoplasms, as well as bone abnormalities. The current findings demonstrate that missense mutations outside the GRD are not solely associated with a mild phenotype.

Clinically relevant NF1 genotype-phenotype correlations exist and understandably are more likely found within the class of missense mutations. Identification of mutation-specific genotype-phenotype correlations depends however on datasets with a large number of individuals, preferentially post-pubertal, carrying the same non-truncating constitutional mutation, with the associated phenotype recorded in a standardized way. As there are only a limited number of truly recurrent non-truncating mutations, prioritization on patients carrying such recurrent mutations is indicated. Although each of the recurrent mutation affects individually only a small percentage of NF1 patients, together they may affect counseling and surveillance in a significant fraction of the NF1 population.

### **Dr Rick van Minkelen, Rotterdam, Netherlands**

Dr. Rick van Minkelen received his PhD in 2008 at the Leiden University Medical Center (LUMC, the Netherlands) on the study of genetic risk factors for venous thrombosis. He is a Clinical Laboratory Geneticist (CLG), certified by the European Board of Medical Genetics and the Dutch Society for Clinical Genetic Laboratory Diagnostics, at the department of Clinical Genetics of the Erasmus Medical Center (Rotterdam). He has a special interest in Neurofibromatosis type 1 (NF1) and related disorders. He is the curator of the NF1 LOVD database (<http://www.lovd.nl/NF1>) for sharing genetic variants and a member of the ENCORE expertise center for neuro-developmental disorders.



#### **Mutation Databases**

A brief overview of mutation databases of RASopathy related genes is given. How can these database help us in classifying variants found in our analyses? How can these databases be accessed and how should we use these databases? What are the benefits and the pitfalls? How can we improve these databases by sharing our data and how to do so?

### **Professor Gareth Evans, Manchester, UK**



Professor Evans has established a national and international reputation in clinical and research aspects of cancer genetics, particularly in neurofibromatosis and breast cancer. He has developed a clinical service for cancer genetics in the North West Region of England, which is nationally regarded. He is an important opinion leader nationally through membership of committees and was chairman of the NICE Familial Breast Cancer Guideline Development Group (2002-2010) and is now clinical lead (2011-). He lectures throughout the UK and internationally on hereditary breast cancer and cancer syndromes. He has given plenary lectures at many international meetings including the International Congress of Human Genetics and two invited lecture tours across Australia (1995, 2001). He has developed a national training program for clinicians,

nurses and genetic counsellors in breast cancer genetics and established a system for risk assessment and counselling for breast cancer in Calman breast units implemented through a training course (1998-2011).

He has published 690 peer reviewed research publications; 259 as first or senior author. He has published over 100 reviews and chapters and has had a book published by Oxford University Press on familial cancer. He has an ISI web of knowledge H-index of 92 and a google scholar H-index of 126 having only published his first article in 1990. In the last 5 years he has raised over £35 million in grants for multicentre and local studies – approximately £31 million to Manchester. He is Chief Investigator on two (£1.59 & £1 million) NIHR program grant (2009-2014 and 2016-2020) on breast cancer risk prediction and also has an NIHR RfPB grant as CI (2011). He has led a successful bid for a nationally funded NF2 service (£7.5 million pa) that started in 2010 and is involved in the national complex NF1 service. He is theme lead and cancer lead on the All Manchester NIHR Biomedical Research Centre worth £28.5 Million (2016-2020).

#### Research interests

- inherited breast and ovarian cancer and its imaging
- Neurofibromatosis types 1 and 2 and imaging
- Other inherited tumour predispositions

#### **Neurofibromatosis type 2 (NF2)**

NF2 is an autosomal dominant tumour predisposing condition caused by mutations in the *NF2* gene on chromosome 22. Individuals who inherit a mutant copy inevitably develop schwannomas on the vestibular nerves at some time in their lives. Most individuals develop bilateral disease in addition to schwannomas on other cranial and spinal nerve roots. Meningiomas affect about 70% of individuals at some time in their lives and low grade ependymomas are also common especially in the cervical spine. Ocular involvement consists of cataracts which rarely require surgery and retinal hamartoma disease. Most NF2 patients currently become deaf and many have significant other handicap. More than 50% of NF2 patients are the first to be affected in their family (*de novo* mutation).

Since the identification of the *NF2* gene in 1993, over 4,000 genetic tests have been carried out on NF2 affected individuals worldwide (>1000 in Manchester). The mutation detection rate in leukocyte DNA depends on which generation is tested in a family. Using sequence analysis we have identified a mutation in a member of the second generation of families with NF2 in 142/149 (95%), 31/142 (22%) had deletions or duplications detectable on MLPA; in 7 (9%) no mutation was identified. In simplex cases (i.e., a single occurrence in a family) the mutation detection rate is around 55-60% (516/913). About 30% of mutations are not detected due to mosaicism. We have currently identified 203 mosaic patients, half by analysis of tumour, where the mutation is not detectable in blood, although we can now detect below 1% with NGS. There are strong genotype-phenotype correlations with type and position of the mutation being associated with disease severity. Truncating mutations particularly in exons 2-13 confer the most severe phenotype whereas missense mutations and splice site mutations (8-15) and truncating mutations in exons 1 & 14-15 are associated with milder disease and near normal life expectancy.

There is now considerable overlap with the related schwannomatosis condition. Schwannomatosis is characterized by multiple non-intradermal non-vestibular painful schwannomas. About 65% of familial and 30% of sporadic schwannomatosis is due to mutations in *SMARCB1* and *LZTR1*. However *LZTR1* mutations are associated with a probably >10% chance of a vestibular schwannoma (VS) and as many individuals with schwannoma only disease with a unilateral VS have germline constitutional *LZTR1* mutations as non-mosaic NF2 mutations.



### **Dr Anup Raji, Manchester, UK**



Raji Anup completed BSC Hons Nursing from All India Institute of Medical Sciences New Delhi India in 2000 and further postgraduate studies at Manchester University. From 2001 to 2011 worked at Manchester University Hospitals in adult orthopaedics and ENT. In 2012 Raji joined the NF1 service as research and Clinical Specialist Nurse and moved to NF2 in 2013. Raji currently works as the lead nurse for the Manchester NF2 service lead by Prof Gareth Evans; involved in on-going research and developments, co-ordination and management of NF2 patients in North West England, patients on Bevacizumab treatment, patients with hearing implants and contributed to NF2 related publications.

#### **Role of NF2 Clinical Nurse Specialists**

NF2 is a long term and life limiting condition where patients develop multiple nervous system tumours, mainly vestibular Schwannomas. Clinical Nurse Specialists (CNS's) have a pivotal role in supporting patients through their NF2 journey. Patients face various co-morbidities in their life time, such as, progressive hearing loss, visual impairment and neurological disability. The genetic implications can be far reaching for them and their family. Management is not just focused on medical or surgical interventions but is around providing best quality of life and helping them adjust to a diagnosis of NF2 and all this entails. This involves a holistic approach to care considering various aspects of a patient's life such as social, emotional, family, employment and personal commitments. CNSs are keyworkers who coordinate various services and inform, advise and support patients on clinical as well as practical issues, with the aim of providing positive patient outcome. There are clinical pathways set by NCG for managing NF2. NCG also specifies protocols for patients receiving Bevacizumab treatment. This includes timely investigation, MDT discussions, sticking to treatment protocols, and collecting and feedback on data.

The CNS role is central to meeting these demands. Execution of clinical pathways should include a professional who has the ability to look at the system as a whole and can employ a multitude of competencies while maintaining a sphere of influence over patients and families, and the system.

### **Dr Vijaya Ramesh, Massachusetts, USA**



Dr. Ramesh is a Professor of Neurology (Genetics) at Harvard Medical School and an Associate Neurologist at MGH. She obtained her Ph.D. from University of Madras, India and completed postdoctoral training in the laboratories of James Gusella (MGH) and Dr. Vivian Shih (MGH). She is a member of the Center for Genomic Medicine at MGH. Ramesh laboratory has been investigating the pathophysiology of Neurofibromatosis 2 (NF2) and Tuberous Sclerosis Complex (TSC) for more than two decades. Her lab employs molecular, genetic, cell signaling and biochemistry techniques in disease-relevant human cells to discover pathways and mechanisms of pathophysiology in NF2 and TSC. The work on NF2 in human arachnoidal and meningioma cells discovered that NF2 protein merlin is a novel negative regulator of mTORC1/mTORC2 signaling. This work has been translated into clinical trials for NF2 and sporadic meningiomas. Ramesh lab has also established CRISPR-Cas genome editing technology in

human arachnoidal cells, Schwann cells and iPSCs and has used this technique to create/correct mutations in NF1, NF2, TSC1 and TSC2 generating isogenic sets of human lines for drug screening and other research efforts.

#### **Drug Development for NF2**

Meningiomas (MN) that arise from the arachnoidal/meningeal layer of the brain are the most common of all primary brain/CNS tumors. Neurofibromatosis 2 (NF2)-associated MN and ~50-60% of sporadic MN show bi-allelic NF2 inactivation and loss of NF2 tumor suppressor protein. Surgery is the only treatment as these tumors are non-responsive to conventional chemotherapies. We previously showed aberrant constitutive activation of mechanistic target of rapamycin complex 1 (mTORC1) signaling upon NF2 loss, which led to clinical trials with rapalogs (RAD001/everolimus) for NF2. More recently, we demonstrated that NF2 loss

also constitutively activates a distinct mTORC2-SGK1-NDRG1 signaling axis, and treatment of NF2-null MNs using dual mTORC1/mTORC2 inhibitor AZD2014 decreased proliferation with greater efficacy than rapamycin. These results have led to ongoing clinical trials with AZD2014 in collaboration with Dr. Scott Plotkin for NF2 meningioma. To understand other pathways dysregulated in NF2 tumor cells, particularly druggable kinases that may lead to improved therapeutic strategies for NF2, we performed a large-scale kinome screen using multiplex inhibitor beads coupled with mass spectrometry (MIB/MS) on our isogenic CRISPR/Cas9-modified human arachnoidal cells (ACs), NF2-expressing vs NF2-null. In NF2-null ACs, MIB/MS identified elevation of several kinases including members of the erythropoietin-producing hepatocellular (EPH) receptor tyrosine kinase (RTK) family EPHA2, EPHA4 and EPHB1, as well as c-KIT. We validated increased expression/activation by immunoblotting and observed robust pEPA2(S897), pEPHB1(Y594) and downstream pSrc/SFK(Y416) in NF2-null ACs and MN cells, and found increased transcription of *EPHA2* and *EPHA4* in NF2-null ACs. EPHA2 is often overexpressed/upregulated in human cancers, and our mechanistic studies revealed that phosphorylation of oncogenic EPHA2(S897) upon NF2 loss was MEK/MAPK-dependent. Treatment with the multi-kinase inhibitor dasatinib significantly inhibited pEPA2, pEPHB1, KIT and Src/SFK in NF2-null ACs and MN cells with minimal effect on mTORC1/2 signaling. Conversely, mTOR inhibitor strongly blocked mTORC1/mTORC2 pathways with no effect on EPH-RTK or Src/SFK targets. This activation of independent downstream pathways upon NF2 loss led us to test effects of combination of mTOR inhibitor with dasatinib, which revealed synergy in NF2-null ACs and primary MNs. Taken together, in addition to mTORC1/2, we for the first time show upregulation of EPH-RTK, SFK and c-KIT pathways upon NF2 loss, supporting a potential therapeutic approach to co-target mTORC1/2 and EPH-RTK/SFK pathways as a novel, more effective strategy for NF2-deficient meningioma.

### **Dr Jaishri Blakeley, Baltimore, USA**



Dr. Jaishri Blakeley is Associate Professor of Neurology, Oncology and Neurosurgery, director of the Johns Hopkins Comprehensive Neurofibromatosis Center (JHCNC) and director of the Neurofibromatosis Therapeutic Acceleration Program (NTAP). NTAP was founded in 2012 to harness intellectual power, essential resources and the power of collaboration to develop effective therapies for the nerve sheath tumors afflicting patients with neurofibromatosis type 1 (NF1). Dr. Blakeley is also an active member of the Department of Defense Neurofibromatosis Clinical Trials Consortium where she serves as the Johns Hopkins site principle investigator and committee chair for Schwannomatosis, a member of the executive committee for the Response Endpoints in Neurofibromatosis and Schwannomatosis International Consortia where she helps develop and validate endpoints for clinical trials addressing NF1, NF2 and Schwannomatosis and a co-

investigator on the first dedicated Specialized Programs of Research Excellence award focused on NF1. She was the co-chair of the 2015 CTF International Neurofibromatosis Conference and the 2016 Society for Neuro-Oncology Education day and has leadership roles at the American Society for Clinical Oncology, the Society for Neuro-Oncology and the American Academy of Neurology (currently chair of the Neuro-Oncology section). She is also invested in mentoring the next generation of physician scientists through the Francis Collins Scholars Program (through NTAP) and as the director of the UCNS Neuro-Oncology Fellowship at Johns Hopkins. Dr. Blakeley's research expertise is in the development of clinical trials for nervous system tumors and specifically, early clinical-translational studies including tumor pharmacokinetic and pharmacodynamic investigations, imaging biomarkers for rare tumors and incorporation of patient focused, functional endpoints into efficacy studies. These efforts are all in the service of improving the outcomes for the patients for whom Dr. Blakeley provides care as an active clinician in neuro-oncology with a focus on neurofibromatosis. The quality of her patient care and her contributions have been recognized with several awards including the Thomas Preziosi Award for Clinical Excellence in Neurology at Johns Hopkins, the Frank Ford Memorial Neurology Teaching Award at Johns Hopkins, the Neurofibromatosis Mid-Atlantic "Make a difference award" and the Children's Tumor Foundation Humanitarian Award.

### **Clinical trials and clinical management for NF2**

Neurofibromatosis type 2 (NF2) is a neurogenetic syndrome manifest by schwannomas effecting cranial, spinal and peripheral nerves. Intracranial or paraspinal meningiomas and low grade ependymomas are also commonly encountered. These tumors are histologically benign, however, their multiplicity, relentless growth and involvement of key anatomic regions of the nervous system result in profound neurologic morbidity. As the majority of patients present in early adulthood with multiple tumors but relatively focal symptoms (i.e. hearing loss or vision change), the goal of clinical care (and clinical trials) is to identify therapies that minimize

the impact of all of these tumors on normal nervous system function for as long as possible. The hallmark of NF2 is bilateral vestibular schwannoma (VS) and the vast majority of people with NF2 will have some degree of VS related hearing loss by their third decade. Surgery is the mainstay of treatment for sporadic VS, but often results in permanent cranial nerve injury (impacting hearing, facial nerve and swallow function) and may not control VS long term in people with NF2. Radiation therapy (RT) is the next most common therapy for sporadic VS, but has uncertain benefit for control of tumor progression and introduces the possibility of both short term neurologic worsening as well as a risk for late malignant conversion. As such a great deal of effort is dedicated to clinically monitoring VS size and hearing function over time and many of the clinical trials to date have had either VS radiographic volume or hearing as assessed by word recognition score as the primary outcome. Meningiomas are another major concern in NF2 as these can be multiple and effect critical areas (e.g. skull base, sagittal sinus, paraspinal) causing multiple presentations of neurologic morbidity. Surgery is first line therapy for both sporadic and NF2 associated meningiomas when feasible. Again, here the role of RT is less certain in NF2-associated meningioma. Hence, this is the second greatest focus of both clinical management and clinical trial development. Ependymomas are the rarest tumors in NF2 and generally do not require intervention, but in select cases contribute to myelopathy and require surgery or possibly off-label drug therapy. Finally, there is a variable rate of neuropathy in patients with NF2 that can result in slowly progressive sensory and motor deficits. Whether this is a primary neuropathy or secondary to diffuse schwannoma involvement is unclear. Clinical management is based on assessment of the relative contribution of all of these processes to the function of an individual patient. Therapeutic interventions are pursued only as indicated to maximize function and slow the progression to loss of function. Data from recent clinical trials and clinical observations from practice will be presented.

### **Professor Scott Plotkin, Boston, USA**



Dr Scott Plotkin, MD, PhD, is a Professor of Neurology at Harvard Medical School and is Director of Cancer Neurology at Massachusetts General Hospital. He graduated magna cum laude from Harvard University and received an MD and PhD in neuroscience from Tulane University School of Medicine. He completed his internship in internal medicine at Tulane and then neurology residency at Massachusetts General Hospital and Brigham & Women's Hospital in Boston, MA. Upon completion of his residency, Dr. Plotkin completed a clinical fellowship in neuro-oncology at Massachusetts General Hospital and was a post-doctoral fellow at the Schepens Eye Research Institute of Harvard Medical School.

Dr Plotkin joined the faculty of Harvard Medical School in 2003 in the Department of Neurology. He is currently Director for the Family Center for Neurofibromatosis as well as director of the MGH/DFCI/BWH Neuro-Oncology Fellowship program. Dr. Plotkin's research focuses on developing clinical trials for patients with NF1, NF2, and schwannomatosis. He has served as principle investigator on single and multi-center clinical trials and is an active member of several national consortia. In 2011, he cofounded the Response Evaluation in Neurofibromatosis and Schwannomatosis (REINS) International Collaboration. This collaboration has published consensus recommendations for clinical trial endpoints in trials for NF patients and continues to work closely with the FDA, Cancer Therapy Evaluation Program, and other agencies.

### **Schwannomatosis**

Schwannomatosis is the third major form of neurofibromatosis. The condition shares many features with neurofibromatosis 2 (NF2) including a predisposition to formation of schwannomas and meningiomas. This phenotypic overlap helps explain why schwannomatosis was not clinically delineated from NF2 until the 1990s. The diagnostic criteria for schwannomatosis have evolved over time and are likely to be updated in the near future to incorporate new information about the clinical features and genetic etiology of the condition. Cross-sectional studies indicate that most patients with schwannomatosis (85%) have sporadic disease without clinically affected family members. The remainder (15%) have familial disease characterized by autosomal dominant inheritance pattern. Genetic studies have shown that schwannomatosis is caused by germline mutations in the *SMARCB1* and *LZTR1* genes, although a significant proportion of patients (particularly sporadic patients) have no identified germline mutations. Collaborative efforts are underway to find additional causative genes. Spinal and peripheral schwannomas are common in schwannomatosis; patients occasionally have intracranial schwannomas or meningiomas and rarely, patients may have unilateral (but not bilat-

eral) vestibular schwannomas. The standard treatment for symptomatic schwannomas is surgery. However, the main issue endorsed by patients is chronic pain which affects about 70% of individuals. Pain control is too often inadequate despite aggressive treatment with multiple classes of pain medications. Attention to anxiety and depression is essential given high rates of these comorbidities in patients with chronic pain. Clinical trials for schwannomatosis-related pain are in development.

### **Professor Eric Legius, Leuven, Belgium**



Eric Legius is a clinician scientist with important clinical responsibilities. He was the head of Human Genetics Department of the University of Leuven till 2016 and he is currently the clinical director of the Center for Human Genetics of the University Hospital of Leuven. His research is targeted towards neurofibromatosis type 1 and related conditions. The research group contributed successfully towards the understanding of the molecular aetiology of a number of tumours in NF1 such as benign neurofibromas, gastrointestinal stromal tumours (GIST), and glomus tumours of the digits. The group was also involved in the molecular and cognitive characterization of the NF1 microdeletion region. Other projects are NF1-related oncogenesis (molecular study of malignant peripheral nerve sheath tumours and atypical neurofibromas) and a clinical trial to improve cognitive aspects in children with NF1 using Simvastatin treatment (NF1-SIMCODA trial together with Erasmus University Rotterdam). The research group is now participating in a clinical trial with Lamotrigine for the treatment of cognitive problems in children with NF1 (NF1-EXCEL together with Erasmus University Rotterdam). We are also involved in behavioural research in NF1 regarding autism spectrum disorder. The research group recently initiated a study on bone abnormalities in children with NF1 with a specific emphasis on the biological mechanism of congenital tibial bowing resulting in pseudarthrosis. In 2007 the research team identified a new condition resembling neurofibromatosis type 1, now known as Legius syndrome (autosomal dominant condition caused by a heterozygous mutation in SPRED1). The group is using animal models to gain insight in the importance of SPRED1 and the RAS-MAPK pathway for cognition.

### **Atypical Neurofibromas and MPNSTs in NF1**

Individuals with NF1 have an increased risk for malignant peripheral nerve sheath tumours (MPNST). It is estimated that the life time risk for MPNST might be as high as 15 % (Reilly *et al.*, 2017). Neurofibromas develop as a consequence of a second hit in the *NF1* gene in Schwann cells. If this happens prenatally in Schwann cell precursor cells than this leads to a plexiform neurofibroma. In addition to a second hit in the *NF1* gene, MPNSTs are characterized by a large number of copy number aberrations, and mutations in *TP53*, *CDKN2A* and genes from the polycomb repressor complex type 2 (PRC2) (De Raedt *et al.*, 2014). Individuals with a typical 1.4 Mb deletion of the *NF1* region, including *SUZ12* (a PRC2 gene), have an increased risk for MPNST (De Raedt *et al.*, 2003), as well as individuals who received previous radiation therapy and individuals who have atypical neurofibromas. Atypical neurofibromas usually arise as faster growing nodular lesions in pre-existing plexiform neurofibromas and are characterized by regions of hypercellularity and nuclear atypia. They show loss of a region on the short arm of chromosome 9, harbouring the *CDKN2A* and *CDKN2B* genes and are premalignant tumours with a high risk for malignant degeneration (Beert *et al.*, 2011). These tumours are now labelled as atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP) (Reilly *et al.*, 2017).



### Dr Michael Fisher, Philadelphia, USA



Mike Fisher is Associate Professor of Pediatrics, Chair of the Neuro-Oncology, Section in the Division of Oncology at The Children's Hospital of Philadelphia (CHOP) and the Director of the Neurofibromatosis (NF) Program at CHOP.

His research focuses on identifying new treatments and novel biomarkers (particularly using new imaging modalities) and exploring functional outcomes for children with tumors associated with NF1. Dr. Fisher is Chair of the Steering Committee of the Department of Defense NF Clinical Trials Consortium. He is Chair of the Visual Outcomes Committee and member of the Steering Committee for REiNS (Response Evaluation in Neurofibromatosis and Schwannomatosis), an international effort to develop standardized outcome measures for clinical trials. In addition, he serves as co-leader

of a CTF-funded, large, international, multi-institutional, prospective longitudinal study of patients with newly diagnosed NF1-associated optic pathway glioma, and is co-PI of the NF1 Low Grade Glioma Synodos project.

### NF1 tumours/OPG

Optic pathway gliomas (OPGs) occur in 15-20% of children with neurofibromatosis type 1 (NF1), leading to visual deficits in up to half of these individuals. Determining which tumors can be observed without treatment is as important as determining which require treatment. In most cases, the goal of treatment is to preserve vision, but predicting which tumors will cause vision loss is challenging. The ability to predict impending vision loss could potentially revolutionize care of these patients and improve overall visual outcomes. When therapy is indicated, chemotherapy continues to be the mainstay of treatment, but little is known about the visual outcomes following treatment. The management of these tumors including treatment indications, therapeutic approaches, visual assessments, and potential biomarkers of vision will be discussed.

### Dr Ian Frayling, Cardiff, UK



Ian qualified in Clinical Medicine at Cambridge. After initial training in all branches of pathology he studied DNA repair by mutM and mutY for his PhD. He is the only Genetic Pathologist in NHS service, at the Institute of Medical Genetics, University Hospital of Wales, Cardiff.

In 1993 in the Family Cancer Clinic at St Mark's Hospital, London he established APC gene testing in familial adenomatous polyposis, microsatellite instability (MSI) and gene testing in Lynch syndrome and PTEN gene testing for Cowden's syndrome. With Ian Tomlinson and Naz Rahman he identified the locus responsible for Hereditary Mixed Polyposis Syndrome, and with Ian Tomlinson that the position within the APC gene of an inherited mutation is itself a major modifier of polyposis severity. Back in Cambridge, in 1998 he established the first clinic in East Anglia for familial bowel and related cancers, and associated testing of colorectal cancer genes, MSI and (with Mark Arends) immunohistochemical (IHC) testing of tumours. He also played a part in the identification of human mutY homologue (MUTYH) as the second gene causing adenomatous polyposis. He now concentrates on mutation interpretation, genotype-phenotype correlations and systematic testing of incident cancers to identify hereditary cases. <https://www.nice.org.uk/guidance/dg27> He is a national External Quality Assessor of mismatch repair protein IHC, an Honorary Senior Clinical Research Fellow at Cardiff University and a Visiting Chief Investigator at Cancer Council New South Wales.

Ian is a member of Council and the Variant Interpretation Committee of the *International Society for Gastrointestinal Hereditary Tumours* (InSiGHT) – now recognised as the first *ClinVar Expert Panel*. He is also a member of the steering group of the *Prospective Lynch Syndrome Database* [www.lscaris.org](http://www.lscaris.org), Honorary Medical Adviser to *Lynch Syndrome UK*, Treasurer of the *UK Cancer Genetics Group*, a member of Faculty of the *Collaborative Group of the Americas on Inherited Colorectal Cancer*, a member of the *Human Genome Variation Society*, and the *European Board of Laboratory Medicine*. Earlier this year Ian was conferred with Honorary Fellowship of the *Faculty of Pathology of the Royal College of Physicians of Ireland* in recognition of his outstanding lifetime contribution to the practice of pathology, and he is also the 2017 recipient of the triennial *Association of Clinical Pa-*

thologists Dyke Foundation Medal.

### **Breast cancer in NF type 1 is a function of the type of NF1 gene mutation and age of onset.**

**Background:** Neurofibromatosis type 1 (NF1) predisposes to breast cancer (BC), but no genotype-phenotype correlations have been described.

**Methods:** Constitutional NF1 mutations in 78 NF1 patients with breast cancer (NF1-BC) were compared with two reference datasets: the NF1 LOVD and 'UAB' (Messiaen and Wimmer, 2008).

**Results:** There was 1.52 / 1.85-fold over-representation of nonsense mutations (NS) and no large deletions in NF1-BC ( $p = 0.047$  vs LOVD /  $p = 0.0012$  vs UAB). Over-representation of NS was greater (1.58 / 1.95) in those with BC  $\geq 50y$  and less in those  $< 50y$ , whereas 91% of missense mutations (MS) occurred in those with BC  $< 50y$ , with 50% of MS predicting a change from a leucine ( $p = 0.048$ ) and 86% a change to either a proline or arginine ( $p = 0.0004$ ), with some evidence of MS clustering in the CSRD ( $p = 0.09$ ). Six pairs and one trio of NF1-BC cases had mutations predicting the same effect on neurofibromin ( $p = 1.93 \times 10^{-11}$  /  $1.47 \times 10^{-5}$ ). Eighteen cases had BRCA1/2 testing, revealing one BRCA2 mutation.

**Discussion:** The observations of an excess of NS, non-random MS, multiple mutations in common between cases and the absence of large deletions all point to a particular subset of NF1 mutations increasing NF1-BC risk. An independent report that amplification is the most frequent NF1 mutation in sporadic BC supports this being a due to specific mutations conferring gain of neurofibromin function. Regarding NS in particular, this effect may be due to reduced stimulation of nonsense-mediated decay by some NS leading to expression of truncated protein conferring a dominant-negative gain of function. A prospective clinical-molecular study of NF1-BC needs to be established to confirm this, but patients with whole gene deletions, at least, do not appear to have an increased risk of BC, and regardless of NF1 mutation status NF1-BC patients warrant testing of other BC-predisposing genes.

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### **Professor Meena Upadhyaya, Cardiff, UK**



Professor Meena Upadhyaya obtained her PhD from Cardiff University and gained Fellowship of the Royal College of Pathologists (FRCPath) from Royal College of Pathologists, London. She is a Distinguished Professor (Hon) of Medical Genetics at Cardiff University. She has led NF1 and FSHD research in Cardiff and has an international reputation in her fields of research. She has made substantial contributions to the molecular understanding of a number of genetic conditions, including neurofibromatosis type 1 (NF1), facioscapulo-humeral muscular dystrophy (FSHD), Legius syndrome, Charcot Marie Tooth disease, Duchenne Muscular Dystrophy, Sotos syndrome, Hunters syndrome inter alia. Professor Upadhyaya has published over 200 papers in peer reviewed journals and co-edited three books and is on number of Committees. She has supervised numerous under-graduate, post-graduate and post-doctoral fellows. She is also actively involved

with a number of charity and community-based projects. She was recently awarded Officer of the Most Excellent Order of the British Empire (OBE) for her contributions to Medical Genetics and the Asian Community in Wales. She has also received the Saint David's award by the First Minister of Wales.

### **The NF1 somatic mutational landscape in sporadic human cancers**

Neurofibromatosis type 1 (NF1) is an autosomal dominantly-inherited tumour predisposition syndrome. Heritable constitutional *NF1* gene mutations result in RAS/MAPK pathway dysregulation and are causative of NF1. The major known function of the *NF1* gene product neurofibromin is to downregulate RAS. NF1 exhibits variable clinical expression, being characterized by benign cutaneous lesions including neurofibromas and café-au-lait macules, as well as a predisposition to various types of malignancy, such as breast cancer and leukaemia. Capitalizing on the availability of next-generation sequencing data from many cancer genomes and exomes, we review current knowledge of somatic *NF1* mutations found in a wide variety of tumours associated with many different tissues, including skin, breast, ovary, lung, brain, colorectum, urothelium, neuroendocrine cells and leukaemias, to better understand their broader role and significance. The ultimate aim being to exploit such mutation data in a diagnostic and therapeutic context. Given neurofibromin's key regulatory role in the RAS/MAPK pathway, acquisition of somatic *NF1* mutations confer drug resistance in tumours, for example *NF1*-associated drug resistance to BRAF, EGFR inhibitors, tamoxifen and retinoic acid, has been observed in melanoma, lung, breast cancers and neuroblastoma. Intriguingly, high rates of somatic *NF1* mutation are detected in cutaneous melanoma, lung cancer, ovarian carcinoma and glioblastoma, tumours not usually associated with NF1, indicating that somatic *NF1* mutations are probably critical 'driver' mutations in multiple cancers. Hence, a better understanding of the mutational landscape of somatic *NF1* mutations should provide novel insights into the patho-physiology of cancer, and underlines the critical role that neurofibromin has in development, far beyond that evident in the tumour predisposition syndrome NF1.

Co-authors: Charlotte Philpott, Hannah Tovell, Ian M. Frayling, David N. Cooper

### **Dr Sheetal Sharda, Bangalore, India**



Dr Sheetal Sharda is a post graduate in Pediatrics and has done her DM in Medical Genetics from Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. She has worked as a Senior Research Associate in the Genetics Unit, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi. She has worked as an Assistant and Associate Professor in Genetics & Metabolic Unit, Post Graduate Institute of Medical Education and Research, Chandigarh for 8 years. She has an experience in clinical genetics of over 13 years.

At present she is working as Senior Consultant in Clinical Genetics in Medgenome Labs, Bangalore which is a Genomics diagnostics laboratory in India.

She has about 30 publications in national and international journals to her credit. Her areas of interest are Dysmorphology, Prenatal Diagnosis counselling and Molecular diagnosis.

**DAY 2: TRANSLATIONAL RESEARCH/CLINICAL APPLICATION, DIAGNOSIS AND  
MANAGEMENT OF RASOPATHIES FOCUSING ON CASE STUDIES**

**Professor Luis Parada, New York, USA**



Luis F. Parada obtained a BS from the University of Wisconsin and a Ph.D. in Biology from MIT, identifying oncogenes in human cancer. He was a Damon Runyon and Helen Hay Whitney Postdoctoral Fellow at the Pasteur Institute. He headed the Molecular Embryology Section at the National Cancer Institute in Frederick, MD from 1988 to 1994 when he moved to the University of Texas Southwestern Medical Center at Dallas as the inaugurating Diana and Richard C. Strauss Distinguished Chair in Developmental Biology, and was Director of the Kent Waldrep Foundation Center for Basic Neuroscience Research. During his time in Dallas, Dr. Parada advanced his studies of nerve cell survival and regeneration, mood disorders, and renewed his attention on cancer with emphasis on the nervous system. His laboratory uses genetic mouse models to study human disease including Neurofibromatosis, cancers of the nervous system, autism, and neural development. In

2015 Dr. Parada moved his laboratory to Memorial Sloan Kettering Cancer Center to assume leadership of the interdisciplinary Brain Tumor Center. In addition Dr. Parada holds the Albert C. Foster Chair and is Professor of Cancer Biology and Genetics. In recognition of his contributions to science, Dr. Parada has been elected to: The National Academy of Sciences; The American Academy of Arts and Sciences; The Institute of Medicine - National Academy of Sciences (National Academy of Medicine); The American Association for the Advancement of Science (AAAS), The Academy of Medicine, Engineering and Science of Texas (TAMEST); and is a life-time American Cancer Society Professor.

**What causes Malignant Peripheral Nerve Sheath tumors to develop?**

MPNSTs are the major cause of mortality in NF1 patients. These aggressive and metastatic tumors are thought to arise from Plexiform neurofibromas as a consequence of mutations in either the P53 or Ink4/arf tumor suppressor genes in addition to NF1 loss. Following surgical resection, radiation therapy and chemotherapy have been used to treat these tumors with very limited success. Doxorubicin, a DNA intercalating agent that inhibits proper DNA replication, is the commonly used chemotherapeutic. Its ability to cause tumor shrinkage is accompanied by a plethora of undesirable side effects including anemia, hair loss and allergic reactions. To better understand the natural history of MPNST, we have developed and studied genetically engineered mouse models that form after mutation of the NF1 and p53 tumor suppressors in progenitors cells from the neural crest lineage. These transformed progenitors readily convert into MPNSTs when implanted in the sciatic nerve of recipient mice. Our ongoing studies provide compelling evidence for several features that may have therapeutic implications. First, we have developed evidence that these tumors grow in hierarchical fashion with an identifiable cancer stem cell (CSC) at the apex of the hierarchy. We can label the CSCs with a GFP reporter transgene. These studies suggest that ablation of the CSC (GFP) population specifically abrogates the ability of the tumors to transplant. Conversely, treatment of the tumor bearing mice with doxorubicin targets the BrdU incorporating tumor cell population but not the GFP positive CSCs. In light of these results, we are in the process of reevaluating the activity of standard chemo and radiotherapies as well as diverse next generation pathway specific inhibitors to determine how CSCs respond.

Daochun Sun and Luis F. Parada



## Professor Nancy Ratner, Cincinnati, USA



Dr Ratner is interested in peripheral nerve tumors that occur in the Neurofibromatoses, NF1 and NF2, and studies the brain in Neurofibromatosis type 1. She uses genomics to study neurofibroma formation and carries out neurofibroma and MPNST preclinical therapeutics. Ratner received her bachelor's degree from Brown University, her doctorate from Indiana University, Bloomington (during which time she was a student in the Neurobiology Course at the Marine Biological Laboratory), and was a postdoctoral fellow at Washington University in St. Louis where she studied Schwann cells in nerve development under Richard Bunge and Luis Glaser. A member of the faculty at the University of Cincinnati 1987 - 2004, she is currently a Professor in the Department of Pediatrics, Cincinnati Children's Hospital, University of Cincinnati, where she holds the Beatrice C. Lampkin Endowed Chair in Cancer Biology. She co-leads the Rasopathy Program and serves as the Program Leader for the Cancer

Biology and Neural Tumors Program in the Cancer and Blood Disorders Institute. She has served on numerous national and international review panels and authored over 100 peer-reviewed manuscripts and 30 reviews. She was awarded the von Recklinghausen Award in 2010, and a Jacob K. Javits Neuroscience Investigator Award (NIH-NINDS Merit Award) in 2014. She has been an active member of the NFTC since its inception.

### Preclinical testing

Plexiform neurofibroma is a major contributor to morbidity in Neurofibromatosis type I (NF1) patients. These incurable peripheral nerve tumors result from loss of NF1 tumor suppressor gene function, causing hyperactive Ras signaling. Cross-species transcriptome analyses of mouse and human neurofibromas and MPNSTs identified global negative feedback of genes that regulate Ras-Raf-MEK- extracellular signal-regulated protein kinase (ERK) signaling in both species. Nonetheless, activation of ERK was sustained in mouse and human neurofibromas and MPNST. Highly selective allosteric inhibitors of MEK were used in a genetically engineered mouse model to test whether sustained Ras/Raf/MEK/ERK signaling contributes to neurofibroma growth in the *Nf1<sup>fl/fl</sup>;Dhh-cre* mouse model (Jessen *et al.*, *J. Clin. Invest.*, 2013). Results from these studies provided strong rationale for testing MEK inhibitors in NF1 clinical trials, and showed that the mouse model is predictive of success in the clinic (Dombi *et al.*, *NEJM*, 2016). We also found that treatment of developing tumors delayed but did not prevent neurofibroma formation. In addition to Ras signaling, macrophages and mast cells infiltrate neurofibroma, and data from mouse models implicates these leukocytes in neurofibroma development (Yang *et al.*, *Cell*, 2008; Prada *et al.*, *Acta Neuropath.*, 2012). Recently, we compared gene expression in inflamed nerves from NF1 models to those with neuro-inflammation that rarely leads to neurofibroma. We identified a chemokine-receptor pathway necessary for neurofibroma formation, and show that neurofibroma formation correlates T cell and DC recruitment. Our data demonstrate that blocking this pathway blocks neurofibroma formation. We uncover a heretofore unappreciated role for T cells/DCs in neurofibroma initiation, and suggest that targeted anti-inflammatory therapy might slow or prevent neurofibroma development in NF1 patients.

Supported by awards from the Neurofibromatosis Therapeutic Acceleration Program, the Children's Tumor Foundation, NIH-NINDS and the DOD Program on Neurofibromatosis.

Dr. Ratner can be reached at [Nancy.Ratner@cchmc.org](mailto:Nancy.Ratner@cchmc.org)

### **Dr Uday Khire, Boston, USA**



Dr. Khire is a scientist and an entrepreneur with international business experience. Dr. Khire co-founded AlloMek Therapeutics in 2011 based on discovery of novel macrocyclic MEK kinase inhibitor at Cheminpharma LLC, a drug discovery services company, founded by him. Prior to founding Cheminpharma in 2007, Dr. Khire worked as a senior scientist at Bayer Research Center. He played a key part in the discovery of "Nexavar", a first in class B-Raf kinase inhibitor (MAP/ERK pathway) which has been approved as a first line therapy for a treatment of kidney and liver cancers. Dr. Khire did post-doctoral research at Purdue University under guidance of Late Prof. H. C. Brown, a Nobel laureate in chemistry. Dr. Khire did another postdoctoral research at University of California, Irvine, where he worked on total synthesis of challenging molecule, roflamycin, a polyol polyene macrocycle, wherein, he devel-

oped interest in macrocycles.

Prior to his post-doctoral position, Dr. Khire received his PhD from National Chemical laboratory in India. Dr. Khire is fascinated by macrocycles and potential of these large cyclic compounds in various therapeutics areas.

### **CIP-137401, a Rationally Designed Macrocyclic MEK 1/2 Inhibitor for Potential Treatment of Laminopathies and Rasopathies Related Genetic Diseases**

Signaling mediated by extracellular signal-regulated kinases 1 and 2 (ERK1/2) is involved in numerous cellular processes. [Mitogen-activated protein kinase kinases](#) (MEK1/2) catalyze the phosphorylation of ERK1/2, converting it into an active kinase that regulates the expression of numerous genes and cellular processes. Inhibitors of MEK1/2 have demonstrated preclinical and clinical efficacy in certain cancers and group of rare diseases called Rsaopathies and Laminopathies. We report the synthesis of a novel, allosteric, macrocyclic MEK1/2 inhibitor, CIP-137401, that potently inhibits ERK1/2 activity in cultured cells and tissues of mice after systemic administration. Mice with dilated cardiomyopathy caused by a lamin A/C gene mutation have abnormally increased cardiac ERK1/2 activity. In these mice, CIP-137401 was well tolerated, improved left ventricular systolic function, decreased left ventricular fibrosis, had beneficial effects on skeletal muscle structure and pathology and prolonged survival. CIP-137401, also displayed potent activity in tumor xenograft models. The novel MEK1/2 inhibitor, CIP-137401, described herein may therefore find clinical utility in the treatment of rare diseases related to Laminopathies and Rasopathies.

### **Professor Brigitte Widemann, Bethesda, USA**



Professor Widemann is the Chief of NCI's Pediatric Oncology Branch, a Deputy Director of NCI's Center for Cancer Research, and head of the Pharmacology and Experimental Therapeutics (PET) Section at the NCI. After obtaining her M.D., from the University of Cologne (Cologne, Germany) in 1986 and completing pediatric residency in 1992 she completed her pediatric hematology/oncology fellowship training at the NCI Pediatric Oncology Branch from 1992 to 1995. She subsequently joined the PET Section and received tenure at NCI in 2009. Her primary research interests are in the development of effective therapies for children and young adults with refractory cancers and genetic tumor predisposition syndromes such as neurofibromatosis type 1 (NF1), and multiple endocrine neoplasia types 2A (MEN2A) and 2B (MEN2B). Dr. Widemann and her colleagues have developed novel imaging methods for NF1-related plexiform neurofibromas, are conducting a longitudinal NF1 natural history study, and pioneered the development of early phase drug treatments for this patient population. Dr. Widemann leads multiple clinical trials of new investigational agents in pediatric refractory cancers and NF1 related plexiform neurofibromas and malignant peripheral nerve sheath tumors. She and her team recently identified substantial clinical activity of the MEK inhibitor se-

lumetinib in children with NF1 and inoperable plexiform neurofibromas. Dr. Widemann also serves as the NCI Pediatric Oncology Branch principal investigator of the Children's Oncology Group Phase I Consortium and of the Department of Defense-sponsored Neurofibromatosis Consortium.

### **Development of effective therapies for benign and malignant peripheral nerve sheath tumours**

Neurofibromatosis type 1 (NF1) is a common inherited disorder characterized by the development of peripheral nerve sheath tumors including plexiform neurofibromas (PN) and malignant peripheral nerve sheath tumors (MPNST). While PN are histologically benign they can result in substantial morbidity including pain, disfigurement and neurologic or functional deficits. Importantly, PN are at risk for transformation to MPNST with a lifetime incidence in NF1 of 15.8%. NF1 related tumors are characterized by activation of the Ras signaling pathway. Several clinical trials aiming at decreasing PN growth have been conducted in the past with limited success. We recently described that selumetinib, a specific MEK inhibitor, resulted in PN shrinkage in children with NF1 and inoperable PN. Subsequently, we developed phase II trials to further characterize the effects of selumetinib in children and adults with PN or cutaneous neurofibromas. In addition, a phase II trial combining selumetinib and an mTOR inhibitor (PI Dr. AeRang Kim, co-PI B. Widemann) was developed for patients with refractory MPNST. Clinical trials with other MEK inhibitors and other targeted therapies are ongoing and in development. Updates on the efforts to develop medical therapies for NF1 PN and MPNST will be presented.

### **Professor Ype Elgersma, Rotterdam, Netherlands**



Professor Ype Elgersma received his PhD in 1995 at the University of Amsterdam on the study of peroxisome biogenesis and protein trafficking in yeast. During his post-doc in the US, he switched his interest towards Neuroscience, studying the mechanisms underlying learning and memory at Cold Spring Harbor Laboratories and UCLA.

In 2002 Ype Elgersma started his laboratory at Erasmus University Medical Center, Rotterdam. The main focus of the laboratory is to understand the mechanism underlying neurodevelopmental disorders. To translate the findings to the clinic, Ype Elgersma is founder and director of the ENCORE expertise center for neuro-developmental disorders, which includes the national referral center for TSC, Angelman Syndrome, Neurofibromatosis, Costello Syndrome, CFC and Fragile X, as well as a neurogenetics and autism clinic. The center is recognized as a national and international referral center. Ype Elgersma is member of a number of scientific advisory boards and won several prizes including the VIDI and VICI award.

### **Learning disabilities in RASopathy: From molecular mechanisms toward clinical trials in neuro-developmental disorders**

Our research is directed at understanding the molecular and cellular mechanisms underlying learning disabilities in neurodevelopmental disorders, and to translate these findings into potential therapies. Our laboratory is particularly interested in neurodevelopmental disorders in the RAS-ERK-MTOR pathway and in Angelman Syndrome. Central to the approach is the use of genetically engineered mice. These mice are studied at the biochemical, cellular and behavioral level. In this way seek to understand the specific function of these genes and proteins in neuronal function, and to develop therapies. These finding are translated to the clinic by running randomized controlled trials involving children with rare cognitive disorders.

### **Professor Pierre Wolkenstein, Paris, France**



Professor Pierre Wolkenstein is MD, PhD, dermatologist at Henri-Mondor Hospital (Assistance Publique-Hôpitaux de Paris). He is Professor at University Paris Est Creteil, Vice-Dean for Academic Affairs and Head of the Department Cancers Immunity Transplantation Infections. He is also the coordinator of the National Referral Centre for Neurofibromatosis in France. Pierre Wolkenstein focused his interest in care, basic, translational, and clinical research in the field of neurofibromatosis, and mainly on neurofibromatosis 1 (NF1). The French Network managed more than 3000 patients with NF1. The papers of Pierre Wolkenstein are centered on severe phenotypes, genotypes-phenotypes correlations, identification of modifying genes and animal models. His index H is 41. From 2-6 November 2018, the French team will organize the first Global Joint Neurofibromatosis Conference.

#### **Neurofibromatosis: Past, Present and Future.**

The Evolving pattern of Recklinghology includes the Past, the Present, and the Future. The Past was essentially dedicated to nosological research leading to define first neurofibromatosis, then neurofibromatosis. After the discovery of NF1 and NF2 genes respectively in 1990 and 1991, genotypes were described in front of a huge variability of phenotypes. The hypothesis of modifying genes was raised in 1993 followed in 2011 by the identification of the first one ANRIL. In 2007 a neurofibromatosis 1 like syndrome, the syndrome of Legius was linked to SPRED1 mutation. In 2008 some familial schwannomatosis were correlated to alteration in INI1 and a few years later to LZTR1.

Beside the progress in molecular biology of neurofibromatosis, the treatments emerged as highlighted by the increase number of trials declared (<https://clinicaltrials.gov>). Evidence of efficacy was published, bevacizumab in neurofibromatosis 2 and recently selumetinib for plexiform neurofibromas. Improvement of surgery led to the first face transplant for plexiform neurofibromas. Animal models are now ready for therapeutic research and the hope of ending neurofibromatosis become concrete thanks to the dynamism of our community.

### **Professor Bruce Korf, Birmingham, USA**



Professor Korf is Wayne H. and Sara Crews Finley Chair in Medical Genetics, Professor and Chair of the Department of Genetics, Director of the Heflin Center for Genomic Sciences at UAB, and Co-Director of the UAB-HudsonAlpha Center for Genomic Medicine. He is a medical geneticist, pediatrician, and child neurologist, certified by the American Board of Medical Genetics (clinical genetics, clinical cytogenetics, and clinical molecular genetics), American Board of Pediatrics, and American Board of Psychiatry and Neurology (child neurology). Dr. Korf is past president of the Association of Professors of Human and Medical Genetics, past president of the American College of Medical Genetics and Genomics, and current president of the ACMG Foundation for Genetic and Genomic Medicine. He has served on the Board of Scientific Counselors of the National Cancer Institute and the National Human Genome Research Institute at the NIH. His major research interests are molecular diagnosis of genetic disorders and the natural history, genetics, and treatment of neurofibromatosis. He serves as principal investigator of the Department of Defense funded Neurofibromatosis Clinical Trials Consortium. He is co-author of Human Genetics and Genomics (medical student textbook, now in fourth edition), Medical Genetics at a Glance (medical student textbook, now in third edition), Emery and Rimoin's Principles and Practice of Medical Genetics (now in 6th edition), and Current Protocols in Human Genetics.

#### **Genome Guided Therapeutics for NF1**

Most efforts at therapeutic development for NF1 have focused in inhibition of abnormal cellular signaling,



especially involving the Ras pathway. Major advances have been made in treatment of some of the tumors associated with NF1, although treatments may have toxic side effects. We have been focused on a different approach, based on restoration of the function of the altered gene or gene product. Although many thousands of NF1 pathogenic variants have been identified, these can be classified into several categories that might be amenable to therapeutic manipulation. We have been creating a variety of model systems to enable drug discovery and testing in a variety of human NF1 pathogenic variants. These include mouse and rat models, induced pluripotent stem cell lines, and a cDNA expression system. Potential therapeutic approaches include nonsense mutation read through, modulation of RNA splicing, ribozyme-mediated RNA repair, correction of function of a misfolded protein, and genome editing. This talk will provide an update on our progress in creation of these model systems in therapeutic development for several types of human NF1 pathogenic variants.

### **Clinical and molecular diagnosis and management of RASopathies- Interactive Session with Panel Discussion**

**Facilitators:** Kate Rauen, Susan Huson, Bronwyn Kerr, Shubha Phadke

#### **Dr Shubha Phadke, Lucknow, India**



Dr Shubha Phadke has an experience of more than 25 years in the field of clinical genetics and laboratory genetics. She runs the first DM in Medical Genetics program in India since 1996 and has contributed to the establishment of the specialty of Medical Genetics in India by training most of the medical geneticists [more than 40] in India. Her interests are pre and postnatal dysmorphism, genetic hematology and she has 262 publications in national & international journals to her credit. 'Genetics for Clinicians' is the book written by her and has popularized genetics amongst clinicians. She is the founding president of Society for Indian Academy of Medical Genetics and founding editor of Genetics Clinics, a three monthly publication of SIAMG. She is on the research committees of ICMR, DBT and on the editorial boards of renowned journals like American Journal of Medical Genetics, Medical Genetics & Genomic Medicine, etc. A two week long yearly training program for clinicians, 'ICMR Course in

Medical Genetics & Genetic Counseling' is held regularly for last 16 years and has introduced more than 500 medical doctors to the fascinating world of medical genetics. She is recipient of prestigious awards like Har-gobind Foundation Fellowship [1994], International Scholarship of Clinical Genetics Society of UK [2009] and Dr I C Verma Outstanding Researcher Award [2016]. Dr Phadke has established Newborn Screening Program for Uttar Pradesh funded by National Health Mission and is successfully running since 2015. Dr Phadke is involved actively with the activities of patient support groups for thalassemia, hemophilia, Down syndrome and rare diseases.

[shubharaopadke@gmail.com](mailto:shubharaopadke@gmail.com)

#### **Dysmorphism Diagnosis of Noonan Syndrome: Clinical to Exome**

Diagnosis of malformation syndromes used to be a clinically challenging activity two decades ago. Experience and skill of pattern recognition were the assets useful in successful diagnosis. Soon the genetic technologies evolved and identification of causative genes gave more meanings and reasons to correct etiological diagnosis. Identification of causative mutation was rewarding to the clinical geneticist and useful to the patient and family. It soon became obvious that genetic and phenotypic heterogeneity is the centre of malformation syndromes. Rasopathies and ciliopathies are examples which evolved over last decade and provided answers to the intrigued clinical geneticists like me about clinically similar syndromes and cases with features overlapping two syndromes. The understanding of genetic etiologies and functional pathways of developmental biology not only helps in diagnosis but also is opening novel treatment strategies. The phenotypes and genotype of Noonan syndrome with PTPN11 mutations will be discussed. Also, limited experience of using exome sequencing for diagnosis of Rasopathies will be presented.

### **Dr Isabel Cordeiro, Lisbon, Portugal**

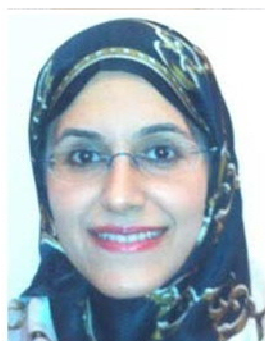


Isabel Cordeiro was born in Lisbon, Portugal. She graduated in Medicine at Lisbon University Medical School. Later, Elizabeth graduated in Paediatrics and Masters in Clinical Genetics. She is an Invited Professor at the Faculty of Medicine. Isabel has now retired as Director of the Serviço de Genética, but is still performing a monthly Genetic Clinics for Neurofibromatosis patients at Hospital Santa Maria

#### **RASopathies: the experience of the Serviço de Genética - Hospital de Santa Maria. Portugal**

The authors reviewed the RASopathies seen in the Department, the investigations and management of its patients.

### **Dr Abeer Alsaegh, Muscat, Oman**



Dr Abeer Alsaegh is the Head of Genetics Department at Sultan Qaboos University and Consultant of Medical Genetics and Cancer Genetics at Sultan Qaboos University Hospital. Her clinical and academic interests include familial cancer syndromes, developmental disorders and autosomal recessive syndromes associated with intellectual disability. She established the cancer genetics clinic in Oman and is an Oman Medical Specialty Board trainer.

#### **RASopathy/Neurofibromatosis disorders (genetic diagnostic yield, challenges and lessons learned so far) - single centre experience from Oman**

Genetics and developmental medicine clinic at Sultan Qaboos University Hospital provides clinical genetics service to all tertiary and secondary hospitals in the country. Aim of this retrospective study was to look at the diagnostic genetic yield of all the referred suspected patients with rasopathy disorders to the service from August 2010 to August 2017. Only 130 patients were referred most of which were from pediatrics. Few patients were referred for neurofibromas type 1 and 2. Diagnostic yield was 30 % after performing a rasopathy panel followed by whole exome sequencing. There were many challenges identified: finding a primary physician to follow up these patients, lack of multidisciplinary clinics, and screening for complications associated with this group of conditions.

### **Dr Joanne Ngeow, Singapore**



Dr Joanne Ngeow, MBBS, MRCP, MPH is Senior Consultant, Division of Medical Oncology at the National Cancer Centre Singapore. Dr Ngeow currently heads the Cancer Genetics Service at the National Cancer Centre Singapore with an academic interest in hereditary cancer syndromes and translational clinical cancer genetics. She was awarded consecutive fellowships by the National Medical Research Council and the Ambrose Monell Foundation to complete formal clinical and wet bench training in Cancer Genomic Medicine at the Genomic Medicine Institute, Cleveland Clinic, Ohio. Dr Ngeow is an Editorial Board Member for Endocrine Related Cancers. Dr Ngeow was awarded the NMRC Clinician Scientist Award in 2017 aimed at understanding how gene-environmental and gene-gene interactions predisposes to cancer initiation and progression.

#### **Clinical Cancer Genetics: Singapore Perspective**

Genetic testing for germline mutations in breast cancer predisposition genes can potentially identify individuals at a high risk of developing breast and/or ovarian cancer. There is a paucity of such mutational information for Asians. Panel testing of 25 cancer susceptibility genes including NF1 analysis was performed for 220 Asian

breast cancer patients or their family members referred for genetics risk assessment. All 220 participants had at least one high-risk feature: having a family history of breast and/or ovarian cancer in first- and/or second-degree relatives; having breast and ovarian cancer in the same individual or bilateral breast cancer; having early-onset breast cancer or ovarian cancer ( $\leq 40$  years of age). We identified 67 pathogenic variants in 66 (30.0%) patients. Of these, 19 (28.3%) occurred in BRCA1, 16 (23.9%) in BRCA2, 7 (10.4%) in PALB2, 6 (9.0%) in TP53, 2 (3.0%) in PTEN, 2 (3.0%) in CDH1 and 15 (22.4%) in other predisposition genes including one patient with a pathogenic NF1 mutation. In addition to breast cancer, this patient had 2 other tumors; all 3 were exomed showing unique second hit mutations in NF1 in the tumors. We will also review challenges and barriers for genetic testing in the Singapore context.

### **Dr Sheela Nampoothiri, Kochi, India**



*Dr Nampoothiri is Clinical Professor & Head of Department, Department of Pediatric Genetics, Amrita Institute of Medical Sciences & Research Centre, Cochin, Kerala.*

Dr Nampoothiri obtained her MBBS with First class from Trivandrum Medical College in 1989, DCH from Institute of child Health, Chennai in 1991 and Completed her Dip NB in Pediatrics in 1993 at Trivandrum Medical College. She obtained an MSc in Medical Genetics from Duncan Guthrie Institute of Medical Genetics, Yorkhill Hospitals, University of Glasgow with first class in 2005. She has worked as a Consultant in Paediatrics for 12 years.

During her work, Dr Nampoothiri has identified a new syndrome 'Nampoothiri syndrome' and is published in American Journal of Medical Genetics, 2011 and now included in London Dysmorphology Database

Dr Nampoothiri has won many awards including a commonwealth Fellowship by the UK in 2004

She is a member of the Task Force on Human Genetics and Genome Analysis program for Department of Biotechnology, Government of India, a Member of the Advisory Board of Genzyme India's "India Medical Advisory Board (IMAB) from 2017 and a Scientific Advisory Committee member of the Comprehensive Care Centre for Neurodevelopmental Disorders, Sree Chitra Tirunal Institute for Medical sciences and Technology, Trivandrum from 2017

### **Experience of Rasopathies : 12 years from a Single Tertiary Care Centre from Kerala**

The 12 year experience of rasopathy from a single tertiary care centre with dedicated team in the field of pediatric cardiology, neurology and pediatric genetics are presented. Amongst the group of rasopathies, the most common type was neurofibromatosis type I (NF1) contributing to 99 patients and mutation study was offered only for 5 patients. They had NF1 and prenatal diagnosis was offered after confirmation of the mutation in them. 4/99 had pseudarthrosis (4%) and one patient had presented with neurofibroma of clitoris which was a very unusual presentation of NF1. Malignant transformation was noted in 6 patients (6%) and 5 of them had optic glioma/ low grade astrocytoma. One boy succumbed following secondaries arising from malignant peripheral nerve sheath tumor which had originated from right ulnar nerve and one patient had acute myeloid leukemia. We do have a NF1 clinic conducted jointly by neurosurgery and neurology departments and all NF1 patients are counselled to review yearly for ophthalmological evaluation and ultrasound study of kidneys and are also counselled to seek medical advice should they have a rapid growth in any of the plexiform neurofibroma or some focal neurological involvement.

The second common rasopathy was Noonan Syndrome. We have a cohort of 156 patients with the phenotype consistent with Noonan Syndrome. Among this cohort 51 patients were found to be mutation proven. PTPN11 was the most common mutation amounting to (88%) and 40% mutation were located in exon 3. Rest of the mutations were linked to RIT1 (6%) and RAF1, LZTR1, SHOC2 contributing to 2% each. 78% of patients among the mutation proven patients had an underlying heart disease and the most common heart disease was pulmonary stenosis amounting to 47.9%. One patient each harbouring a PTPN11 and RIT1 mutation had leukemia.

The other two rare forms of rasopathies encountered were Costello syndrome and Cardiofaciocutaneous syndrome (CFC). Amongst 9 patients who had a phenotype consistent with Costello syndrome, 3 patients were confirmed by molecular study and all three of them had the same mutation (G12S) which is the most



common mutation that is reported in more than 80% cases from the literature. 11 patients had clinical features suggestive of CFC syndrome, among them only two patients were subjected to molecular analysis & one each had a mutation in BRAF & MEK1.

The multidisciplinary approach was extremely fruitful for the overall management and counselling of these patients with rasopathies.

Sheela Nampoothiri<sup>1</sup>, Dhanya Yesodharan<sup>1</sup>, Shwetha Kuthirol<sup>1</sup>, Mahesh Kappanayil<sup>2</sup>, K P Vinayan<sup>3</sup>, Ashok Pillai<sup>4</sup>

1. Department of Pediatric Genetics, Amrita institute of Medical Sciences, Kochi.

2. Department of Pediatric Cardiology, Amrita institute of Medical Sciences, Kochi

3. Division of Pediatric Neurology, Department of Neurology, Amrita institute of Medical Sciences, Kochi

4. Department of Neurosurgery, Amrita institute of Medical Sciences, Kochi

## Dr Shay Ben-Shachar, Israel



Dr Ben-Shachar graduated from The Sackler Faculty of Medicine. He completed residency in pediatrics at Tel Aviv Medical Center and performed a fellowship in medical genetics along with a postdoctoral training at the department of Human and Molecular Genetics at Baylor College of Medicine (Houston, TX) working on *MeCP2* gene and animal models for autism. Since his return to Israel at 2009 he serves as the director of pediatric genetics service and the neurogenetic clinic. He is a part of the Israeli Gilbert neurofibromatosis center- a multi-disciplinary tertiary center dedicated to evaluation and treatment of all aspects of Phakomatosis.

Dr Ben-Shachar research includes both clinical and translational research, concentrated in clinical aspects of NF1 including genotype- phenotype correlations, as well as *NF1* gene structure and function.

## Neurofibromatosis Type 1, RASopathies, and Other Medical Conditions among Children with Cafe-Au-Lait Macules

CALMs are found in other genetic conditions such as Legius syndrome described in about 2% of individuals with  $\geq 6$  CALMs and negative *NF1* gene testing). Although other conditions such as Noonan syndrome, constitutional mismatch repair deficiency syndrome and ring chromosomes, may be associated with CALMs, CALMs are usually not a cardinal feature of these conditions.

The roll of CALMs in these conditions will be discussed. In addition, I will show an algorithm determining the risk of individuals with CALMs to have constitutional NF1. The algorithm was developed using a retrospective data was generated using a machine-learning-based techniques. According to the algorithm, children >29 month-old with at least one atypical CALM or <6 CALMs have a 0.9% (95% confidence interval [CI]: 0-2.6%) risk for constitutional NF1 while children <29 month-old with  $\geq 6$  CALMs have a high risk (80.4%, 95% CI 74.6%-86.2%). It is important to bear in mind that individuals with CALMs not having NF may have one of the other aforementioned conditions necessitating a meticulous clinical evaluation of each individual with CALMs.

## Dr Yemima Berman, Sydney, Australia



Dr Mimi Berman runs the Clinical Genetics Department and NF clinic at Royal North Shore Hospital in Sydney, Australia. Dr Berman provides consultative and management services in the care of adults and children with NF1, NF2, and Schwannomatosis. Dr Berman trained at the Children's Hospital at Westmead, where she worked in the Paediatric NF clinic. She has a PhD in Neurogenetics in the area of muscle performance and metabolism, and is co-chair of the NSW Clinical Genetics Network. Dr Berman is the Medical Advisor to the Australian Children's Tumour Foundation.

We present an overview of the NF clinical service at RNSH, including details of the establishment of a multidisciplinary NF1 skin clinic. Findings from the clinic will be presented, including quality of life outcomes and outcomes of treatment for itch.

**Dr Niby J Elackatt, Organisation for Rare Diseases, India**



Niby J Elackatt is a highly motivated and detail-oriented HGSA certified Associate Genetic Counsellor from Griffith University with more than 7 years' experience in prenatal genetics, oncogenetics, neurogenetics, paediatric genetics, public health genetics/genomics, IVF/PGD counselling, NGS counselling and clinical/graduate education.

RASopathies are known to result in neurobehavioral features as a part of the syndrome. It is important to appreciate the range of psychosocial issues faced by families with genetic conditions which is possible only by understanding the psychosocial typology of these conditions, the "uncertainty" that comes with the diagnosis and understanding the family systems.

Rapid developments in genetic knowledge and availability of genetic tests have raised ethical and legal issues that need to be considered. Counseling and communication with the patient and family about genetic testing should include assessment of the significance of the potential benefits and harms of the test, psychosocial issues associated with medical problems or preexisting issues may be either exacerbated or alleviated by testing. The presence of severe anxiety or other psychopathology should be an indication for further psychological intervention—and not necessarily an indication for genetic testing.

It is important to consider the medical, psychosocial, and reproductive issues that bear on providing the best care. This will require the provider to engage individual families in comprehensive discussions of these issues and to provide them with specific information and recommendations about genetic testing. Because such testing has potential for both great benefit and great harm, and because the availability of tests continues to expand, it is important to address psychosocial, ethical issues along with syndrome management.

### DAY 3: CLINICAL ASPECTS OF RASOPATHIES, CLINICAL TRIALS, PANEL DISCUSSION ON MEK1 INHIBITOR (Selumetinib)

#### Professor Bronwyn Kerr, Manchester, UK



Professor Bronwyn Kerr is a consultant clinical geneticist who has worked in Manchester in the UK since 1995. Her principal research interest has been Costello syndrome, and more recently, other disorders of the RAS/MAPK pathway. She is a member of the Medical Advisory Boards of the International Costello syndrome support group, the Costello Family Support Network and the Noonan syndrome association (UK). She has a number of key publications in this area, and is frequently consulted by national and international colleagues for advice on diagnosis and management in this group of disorders. A particular interest is developing an evidence base for management of rare disorders.

She is a member of the steering group of GenIDA (Genetically determined Intellectual Disabilities and Autism Spectrum Disorders), an on-line registry for patients, families and professionals. She is the lead for the Guideline Development work-stream of the European Reference Network project ITHACA (HP-ERN-2016; 739516), a five year project commencing April 2017. With Dr Emma Burkitt-Wright, she runs a specialist Rasopathy clinic, seeing patients for confirmation of diagnosis and management advice from across the UK.

With Professor Martin Zenker and Marco Tartaglia, she has organised a second yearly European meeting on Rare Disorders of the RAS/MAPK pathway, commencing in 2009. Attracting over 70 attendees, this has been a focus for facilitating European collaboration and research in these conditions

#### Noonan Syndrome

Noonan syndrome (NS) is a common condition, initially characterized by the triad of congenital heart disease, particularly pulmonary stenosis, short stature and recognizable facial characteristics.

NS is a heterogenous disorder. Mutations in PTPN11 account for around 50% and the phenotype most recognizable as NS. The responsible mutation remains unknown in around 20% of diagnosed people.

The major genes and genotype/phenotype correlations are summarised below:

Gene	%	Phenotype
PTPN11	50	Classical NS
SOS1	10-13	Less short stature and intellectual phenotype. Ectodermal prominent
RAF1	5	Cardiomyopathy 95%; lentigines
KRAS	<5	More severe intellectual and more severe ectodermal
RIT1	5	PS, Cardiomyopathy, lymphatic, including prenatal
SHOC2		Loose anagen hair, ectodermal
NRAS		Classic NS
BRAF	<2	Classic NS, greater ectodermal
MAP2K1	<2	Classic NS, greater ectodermal
SOS2		Classic NS
CBL		Increased JMML, moya moya disease
LZTR1		Classic NS
PPP1CB		Like SHOC2

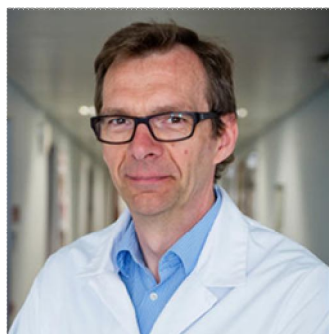
(ref; Noonan syndrome, Gene reviews 2016, JE Allanson, AE Roberts)

Several other very rare variants with a less certain relationship with Noonan syndrome remain under evaluation.

Recent research has found a high incidence of autistic spectrum disorder and attention deficit hyperactivity disorder in children with NS.

In addition to the classic phenotype first described by Jaqueline Noonan, two distinctive phenotypes have been recognized; Noonan like syndrome with multiple lentigines (previously LEOPARD syndrome) and Noonan like syndrome with loose anagen hair (Mazzanti syndrome). Over time however, and with increased availability of gene testing, it is apparent that the manifestations of gain of function mutations in genes of the RAS/MAPK pathway are on a clinical spectrum, with few that are specific to a gene. The diagnosis of NS can be suspected because of a constellation of suggestive features, where short stature and NS associated facial features may be absent.

### Professor Eric Legius, Leuven, Belgium



#### Legius syndrome

Multiple café-au-lait spots (more than 5) are part of the clinical diagnostic criteria for neurofibromatosis type 1 (NF1), which is an autosomal dominant condition. Children with neurofibromatosis type 1 and below the age of 5 years frequently show café-au-lait spots (CALS) as the only diagnostic criterion. If other diagnostic criteria are present such as Lisch nodules, neurofibromas, optic pathway gliomas, and specific bone abnormalities (eg pseudarthrosis) than a formal diagnosis of neurofibromatosis type 1 can be made. Multiple café-au-lait spots might also be seen in a number of other conditions, but it most frequently points to neurofibromatosis type 1 (more than 90% of cases).

It is important to realize that 3-4% of individuals with a formal diagnosis of neurofibromatosis type 1 have Legius syndrome, caused by heterozygous mutations in the *SPRED1* gene (Brems *et al.*, 2007; Messiaen *et al.*, 2009). Individuals with Legius syndrome have multiple café-au-lait spots with or without freckling but they do not show the increased tumor risk as is seen in NF1. Individuals with Legius syndrome do not show the typical choroidal noduli seen by OCT in NF1.

The SPRED1 protein binds with its EVH1 domain to two regions flanking the GAP-related domain of neurofibromin. SPRED1 is important to recruit neurofibromin to the plasma membrane where neurofibromin can downregulate active RAS bound to GTP (Hirata *et al.*, 2016).

### Professor Bronwyn Kerr, Manchester, UK



#### Costello Syndrome

Costello syndrome (CS) was first described in the 1970s by Jack Costello, a New Zealander Paediatrician, as a developmental disability syndrome associated with moderate developmental delay, short stature and macrocephaly, congenital heart disease, loose skin on the hands and feet, distinctive facies and warts at moist surfaces.

Although there were no further reports until the 1990's, clinical studies since have established that this is a disorder with a very distinctive natural history, with severe feeding difficulty being almost universal (necessitating nasogastric or gastrostomy feeding) and associated with failure to thrive and extreme irritability in the first years of life. Ultimate developmental outcome is usually much better than would be anticipated in the early years.

CS has some overlap with both Noonan syndrome and cardio-facio-cutaneous syndrome (CFC). Congenital heart disease and hypertrophic cardiomyopathy are both common. Atrial tachyarrhythmia is very frequent

and may occur in the perinatal period. Growth hormone deficiency, early hypoglycaemia and precocious puberty all occur. Orthopaedic problems, including scoliosis, are also frequent.

CS is due to activating mutations in HRAS, a gene of the RAS/MAPK pathway and an oncogene mutated in 30% of all human cancers. There is overlap between the residues affected in the germ-line mutations causing CS, and somatic mutations recorded in cancer. Most CS patients have a mutation resulting in G12S, with G12A being the next most common.

Cancer in early life is a significant health risk, with a 15% chance of developing cancer, mostly embryonal rhabdomyosarcoma, usually by age 6. Bladder cancer occurs from the teenage years. When cancer occurs, treatment is as in the non-CS population. Expert opinion has suggested a screening protocol based on regular abdominal ultrasound in the first decade, and annual urinalysis from age 10.

Although at its core CS is a relatively homogenous phenotype, a severe neonatal phenotype is recognised, and a cause of early mortality. As new genomic technologies have developed, milder phenotypes, less easily diagnosed as CS, are seen with less common HRAS mutations.

HRAS is important in cell proliferation and aspects of the phenotype reflect that this is abnormal. Benign tumours, papillomata, excess skin, and persisting abnormal head growth causing posterior fossae compression can all result.

Despite very significant delay in early life, most children with CS have mild to moderate developmental impairment, with many attending mainstream school in the primary years. Some young adults have achieved independent supported living.

Although there have been several mouse models of CS, no treatments for aspects of the phenotype have resulted as yet.

### **Professor Katherine (Kate) Rauen, California, USA**



#### **Cardio-fascio-cutaneous Syndrome**

Cardio-facio-cutaneous syndrome (CFC) is a multiple congenital anomaly disorder and is one of the RASopathies. CFC is caused by alteration of activity of the Ras/mitogen-activated protein kinase (MAPK) pathway due to heterozygous germline mutations in protein kinases BRAF, MEK1 or MEK2. KRAS, a small GTPase, has been reported in both CFC and Noonan syndrome so its role in CFC syndrome is unclear at this time. Although CFC syndrome displays phenotypic variability, individuals typically have characteristic dysmorphic features, cardiac defects, ectodermal anomalies and varying degrees of developmental delay. Because of the common pathogenetic mechanism of the RASopathies, CFC syndrome has overlapping features with other RASopathies, most notably Noonan syndrome and Costello syndrome. Because there has been such intense focus on pathway inhibition, small molecular inhibitors such as Raf and MEK inhibitors may be of therapeutic use for RASopathies, especially for CFC.



### **Professor Miikka Vikkula, Brussels, Belgium**



Prof Vikkula obtained his M.D. at the University of Helsinki in 1992 and his Ph.D. in molecular genetics, in 1993. He was a Research Associate at Harvard Medical School 1993-1997, during which time he became interested in vascular and lymphatic anomalies. With his wife, Prof Laurence Boon, Plastic Surgeon, Co-ordinator of the Vascular Anomaly Center, Brussels, the couple discovered the gene for familial venous malformation in 1996, and since then many others. They settled in Brussels in 1997, where Dr Vikkula developed his own laboratory. He obtained a "docentship PhD" in 2000, and was nominated Assistant Professor at the Faculty of Medicine in UCL. He is a member of the Directorate of the de Duve Institute since 2004, and a full professor of Human Genetics since 2013. He has received numerous honours and awards; most recently, the Inbev-Baillet Latour Clinical Prize in 2013. He served as president of the Belgian Society of Human Genetics 2004-2008, and as a member of

the Scientific Program Committee of the European Society of Human Genetics 2008-2012. He is a Member of the Royal Belgian Academy of Medicine since 2012. Prof Vikkula is well known internationally as a major contributor to the understanding of molecular basis of vascular anomalies and lymphedema with >150 peer-reviewed publications and numerous chapters in major bio-medical text books.

#### **Capillary Malformation– Arteriovenous Malformation (CM-AVM)**

Vascular anomalies are localized defects of the lymphatic or vascular system. They are most easily observed on the skin, but can affect any body part. They are divided according to vessel type into arterial, capillary, venous, lymphatic and combined-complex malformations.

The most common vascular malformation is capillary malformation (CM) with a calculated prevalence of 0,3%. They mostly occur sporadically as a single lesion of variable size and localization. Arteriovenous malformation (AVM), on the other hand, is very rare, with an estimated prevalence around 1/10.000. Most AVMs are also localized and occur sporadically. They are the most devastating and difficult to treat vascular anomalies.

Both CMs and AVMs sometimes occur as multifocal lesions in a patient. This is commonly associated with family history of similar vascular lesions, akin to familial association of telangiectasias with AVMs in hereditary haemorrhagic telangiectasia.

We have studied such patients and families, and discovered mutations in the RASA1 gene in over 150 index patients allowing a more precise characterization of the clinical phenotype. Moreover, we recently identified another gene, EPHB4, mutated in more than half of the CM-AVM patients not mutated for RASA1. The first 50 CM-AVM2 patients have demonstrated some clinical differences with CM-AVM1.

RASA1 encodes p120RASGAP, a negative inhibitor of RAS. p120RASGAP is a homologue of NF1. It is also a direct effector of EPHB4. These data label CM-AVM as a RASOPATHY, and highlight the pathogenic importance of the EPHB4-RAS-MAPK signaling pathway in CM-AVM. The loss-of-function mutations in CM-AVM induce activation of the RAS-MAPK pathway, suggesting that repurposing of inhibitors of this pathway may be useful in the future management of CM-AVM patients.

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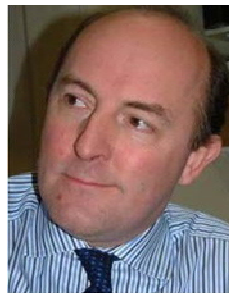
## **Panel Discussion:** Sulemetinib (MEK1/2 inhibitor) in treating patients with NF1

**Facilitator:** Gareth Evans

**Panel:**

Luis Parada  
Eric Legius  
Brigitte Widemann  
Scott Plotkin  
Kate Rauen  
Pierre Wolkenstein  
Mike Fisher  
Nancy Ratner  
Bruce Korf  
Jaisree Blakeley

The MEK inhibitor sulemetinib is the first agent to be shown in clinical trials to have clear evidence of efficacy for a tumour related problem in NF1. An early phase trial in childhood plexiform neurofibromas showed shrinkage in a high proportion of tumours. The roundtable will discuss future possibilities for trials in childhood plexiforms and how these may be designed. It will also discuss treatment potential in adults and in other tumour types in NF1 including optic pathway gliomas.



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### **Dr Anant Tambe, Manchester, UK**



Dr Anant Tambe is a complex spinal surgeon with a special interest in paediatric spinal surgery. He works at Salford Royal Foundation Trust in Manchester which is the largest spine surgery centre in Europe. He also practices at the Royal Manchester Children's Hospital. A significant part of his practice includes correction of complex spinal deformities of the cervico-thoracic and thoracolumbar spine, and he regularly deals with neuromuscular scoliosis, metabolic bone diseases and neurofibromatosis.

#### **Spinal Neurofibromas Surgery**

Spinal manifestations in Neurofibromatosis type 1 occur in almost 10-33% patients. These include deformity, enlarged neural foramina, dural ectasia, spinal neurofibromas and multiple schwannomas, defective pedicles, paraspinal masses, pencilling of ribs and spindling of the transverse process.

Spinal deformity can most commonly affects the thoracic spine but can cause cervical kyphosis, spondylolysis and C1/C2 instability. Kyphosis and C1/C2 instability is associated with neurologic deficits. Neurofibromatosis type 2 does not cause any bone involvement however multiple nerve sheath tumours occur.

Spinal deformities are categorised into dystrophic and non-dystrophic types. Management is based on meticulous clinical assessment, thorough radiological work up with plain radiography and MRI. Occasionally CT scan is essential to assess the extent of bone destruction.

Dystrophic curves have a relentless progression and have a significant negative impact on the quality of life of children. Bracing is usually unsuccessful. Combined anterior/posterior spinal arthrodesis including the entire structural component of the deformity is indicated in most cases, particularly in the presence of associated sagittal imbalance. This should be performed using abundant autologous bone graft and segmental posterior instrumentation to minimize the risk of non-union and recurrence of the deformity. Recently vascularised grafting has been used to mitigate some of the non-union problems.

Non-dystrophic curves can be treated as idiopathic adolescent scoliosis. Higher risk of pseudoarthrosis should be considered whilst planning treatment.

### **Dr Suma Shankar, California, USA**



Dr. Suma Shankar is an Associate Professor in the Department of Pediatrics, Division of Genomic Medicine at UC Davis Medical Center. She is the Director of Precision Genomics and will lead the effort in bringing genomics to every day clinical practice. She is working on integrating genomic medicine with multiple specialties in pediatrics and adults for rare Mendelian diseases and complex disorders. Dr. Shankar is a clinician scientist who received her medical degree from Bangalore Medical College, Bangalore and PhD in Molecular Genetics from University of Iowa, USA. She is an ophthalmologist trained in United Kingdom and is a Fellow of the Royal College of Surgeons (FRCS), Edinburgh and Member of the Royal College of Ophthalmologists (MRCOphth), London. She also completed a fellowship in Medical Genetics at the University of California, San Francisco and is board certified in Medical Genetics by the American Board of Medical Genetics (FACMG). She was faculty in the Departments of Human Genetics and Ophthalmology at Emory University, School of Medicine, Atlanta, USA where she initiated Ocular Precision Health Initiative with biobank and genetic studies for inherited eye diseases for the first time in Georgia. She served as Medical Director for Emory Genetics Laboratory and was primary investigator on a number of clinical trials investigating novel therapies for rare genetic disorders. She has won the Western scholar and Henry Christian Award and Certificate of Excellence in Research from the American Federation Medical Research for research in ocular manifestations in RASopathies. She has a number of publications and several book chapters on genetic testing, ocular genomics, novel enzyme replace-

ment, substrate, and chaperone therapies. Her chief research interests are gene discovery projects and translational research for genetic diseases.

A link to her publications can be found at this URL:

[http://scholar.google.com/citations?hl=en&user=u6FQarEAAAAJ&view\\_op=list\\_works&sortby=pubdate](http://scholar.google.com/citations?hl=en&user=u6FQarEAAAAJ&view_op=list_works&sortby=pubdate)

### **Clinical Trials for RASopathies**

Somatic mutations in the RAS/MAPK signaling pathway are involved in many cancers and have led the way to preclinical tests and clinical trials in RASopathies. Nearly all RASopathies are caused by upregulation of the RAS signaling mediated through the kinases Raf, MEK and ERK. Many drug therapies targeting reduction in the activity of RAS signaling, such as Farnesyl Transferase inhibitors, Raf and MEK inhibitors have been tried in cancer treatment and are potential options for treating RASopathies. There are a number of animal models of RASopathies, that have multiple congenital anomalies and these serve as models for testing drugs that modify the Ras/MAPK signal transduction. A mouse model of Noonan syndrome (NS) caused by germline *Sos1*<sup>E846K</sup> mutation, increases Ras-GEF activity causing sustained Ras activation. These mice exhibit several features of NS such as, small size, facial dysmorphism and cardiac defects, including ventricular septal defect, aortic valvular stenosis and hypertrophic cardiomyopathy as well as reduced life span. A MEK inhibitor (PD032590) was administered prenatally by intraperitoneal injection (IP), 1mg/kg from 7 days post-coitum and postnatally by IP into the nursing female until P9. Pups were then individually IP injected from P10 until P28; this was found to normalize phosphorylation levels of ERK1/2. Further, treated mice showed improved cranial dysmorphism and had milder cardiac defects. These results support the notion that phenotypes can be successfully treated in both the prenatal and postnatal period by manipulating Ras/MAPK activity. MEK inhibitors such as MEK162 has also been tried in adults with Noonan Syndrome who have hypertrophic cardiomyopathy. Currently a prospective randomised placebo-controlled phase 3 therapeutic trial using statins (HMG-COA) reductase inhibitors thought to decrease Ras activity is underway in France. The availability of a number of potential drugs open the possibilities of using systemic therapies after birth to reduce Ras/MAPK activity in Noonan, Costello and Cardiofaciocutaneous syndromes, and, hold the potential to ameliorate the progression of signs and symptoms associated with these disorders. Bringing these therapies to clinical trials necessitates collaboration and effort of multiple teams of researchers, clinicians, private industry, and advocacy organizations.

### **Professor Bruce Korf, Alabama, USA**

#### **Future Directions for RASopathies**



The RASopathies are a diverse group of medical disorders that involve dysregulation of Ras signaling. The specific molecular etiologies are diverse, and phenotypic features for different syndromes are distinct, yet overlapping. An agenda for the future can include focus on research, clinical care, and education. From a research perspective, several questions remain. We do not know the full spectrum of RASopathies, including the various genes involved and the degree of phenotypic overlap. Looking at the similarity and differences in the phenotypes may help reveal pathogenic mechanisms. Questions also remain about the degree of reversibility of specific components of the phenotype. Preclinical test systems and determination of outcomes for future clinical trials are also needed. From a clinical perspective, there is a need for diagnostic criteria, information about natural history, and clinical practice guidelines. Finally, there is a need for education of health providers and patients and families. There are several advocacy groups dedicated to various of the RASopathies, both individual disorders and the group as a whole. Coordination of activities of these groups, and networking of patients and families with the clinical and research community will be important towards improving the quality of life for those affected with the disorders.

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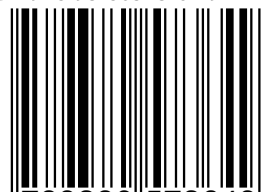


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