Clinical Genomics:
Fundamentals of Variant Interpretation in Clinical Practice
29-31 January 2020

Wellcome Genome Campus,
Hinxton, Cambridge, UK

Course Programme

Wednesday 29 January 2020

10:00-11:00  Registration with morning coffee

11:00-11:20  Welcome and introduction: Principles of genomic medicine
Dr Helen Firth
Cambridge University Hospitals, UK

11:20-12:50  Session 1: Tools for variant interpretation
In this session, you will be introduced to the tools that are used for variant interpretation. You will learn about the fundamental principles of each of the tools, their strengths and weaknesses and how they can be applied using the ACMG framework.

11:20  Setting the scene for variant interpretation: transcripts, annotation and moving from build GRCh37 to GRCh38 including MANE initiative
Dr Sarah Bowdin
Cambridge University Hospitals, UK

11:50  Population data: gnomAD, ExAC, constraint and PEXT scores
Dr Kaitlin Samocha
Postdoctoral Fellow, Wellcome Sanger Institute, UK

12:20  Computational and predictive data. In silico tools including splice tools.
Strength and limitations
Prof Andrew Wilkie
University of Oxford, UK

12:50-14:00  Lunch

14:00-14:40  Session 1 cont: Tools for variant interpretation

14:00  Functional data
Prof David FitzPatrick
MRC Human Genetics Unit, University of Edinburgh, UK
14:20  Segregation data
  Prof Andrew Wilkie
  University of Oxford, UK

14:40-15:15  **Session 2: The ACMG framework**
  During this session, you will understand how to apply your learning from sessions 1 and 2 to the ACMG framework (incorporating the ACGS updates) as a structure to facilitate variant interpretation.

  *Prof Sian Ellard*
  *University of Exeter, UK*

15:15-15:45  **Session 3: Tools used in DECIPHER**
  During this session, you will be introduced to the DECIPHER online resource which integrates variant interpretation tools and the ACMG framework to facilitate and record MDT variant discussion.

  *Dr Julia Foreman*
  *DECIPHER Project Manager, Wellcome Sanger Institute, UK*

15:45-16:15  **Afternoon tea**

16:15-18:00  **Session 4: Putting it into practice – Workshop 1**
  In this first workshop, you will learn how to access the various variant interpretation tools and databases discussed during the day and apply your learning to interrogate genomic variation.

  *Decipher Team*
  *Wellcome Sanger Institute, UK*

18:00-18:45  **Free time**

18:00-18:45  **Opportunity for trainees to have tutorial discussions based on content covered during the day**

  *Dr Sarah Bowdin*
  *Cambridge University Hospitals, UK*
  and
  *Prof Kate Tatton-Brown*
  *ICR/St George’s University, UK*

18:45-19:30  **Pre dinner drinks**

19:30  **Buffet dinner**
Thursday 30 January 2020

Variant interpretation

09:00-09:10  **Introduction to Day 2**

09:10-10:30  **Session 5: Putting it into practice – Workshop 2**
   In this second workshop, you will revise the concepts learnt during day 1 and apply the tools to increasingly complex rare disease genomic variants.

   *Decipher Team*
   *Wellcome Sanger Institute, UK*

10:30-11:00  **Coffee**

11:00-11:40  **Session 6: Risk estimation and penetrance**
   In this session, you will be introduced to risk estimation and penetrance, and the role of genomics in diagnosis and screening.

   11:00  **Risk estimation in genomic medicine: understanding diagnostic and screening tests – the importance of prior risk and penetrance**
   *Prof Andrew Read*
   *University of Manchester, UK*

   11:20  **Introduction to the tolerated population variation calculator**
   *Dr Nicola Whiffin*
   *Research Fellow, Imperial College London, UK*

11:40-13:00  **Session 7: Workshop 3**
   In this session, you will evaluate phenotype and genotype data using DECIPHER ACMG variant classifier, citation tool and clinical fit tool. Each centre to bring 5 illustrative cases. Work in teams to prepare cases for tomorrow morning’s MDT discussion.

   *Decipher Team*
   *Wellcome Sanger Institute, UK*

13:00-14:00  **Lunch**

14:00-15:30  **Session 8: Cardiac genetics: Talk and Workshop 4**
   In this session, you will learn why the interpretation of cardiac genetic variants differs from rare disease variant interpretation and how the ACMG criteria (and component tools/databases) can be applied to cardiac genetic variants.

   **Application of ACMG to cardiac genetics**
   *Prof James Ware*
   *Imperial College London, UK*

   **Workshop**
   *Prof James Ware*
   *Imperial College London, UK*
   *with*
   *Dr Kate Thomson*
   *Oxford University Hospitals, UK*
15:30-16:00  **Afternoon tea**

16:00-18:00  **Session 9: Cancer genetics: Talk and Workshop 5**
In this session, you will learn why the interpretation of cancer genetic variants differs from rare disease variant interpretation and how the ACMG criteria (and component tools/databases) can be applied to cancer genetic variants.

**Application of ACMG to cancer genetics**
*Prof Clare Turnbull*
*Cancer Lead, Genomics England, UK*

**Workshop**
*Prof Clare Turnbull*
*Cancer Lead, Genomics England, UK*
*with*
*Dr Marc Tischkowitz*
*University of Cambridge, UK*
*and*
*Dr Patrick Tarpey*
*Cambridge University Hospitals, UK*

18:00-18:30  **Free time**

18:00-18:30  **Opportunity for trainees to have tutorial discussions based on content covered during the day**
*Dr Sarah Bowdin*
*Cambridge University Hospitals, UK*
*and*
*Prof Kate Tatton-Brown*
*ICR/St George’s University, UK*

18:30-19:15  **Pre dinner drinks**

19:15  **Course Dinner**
### Friday 31 January 2020

**Multidisciplinary interpretation of the genome**

#### Session 10: Integrating phenotype and genotype for safe practice in genomic medicine

This session will focus on the importance of interpreting a genotype in the context of phenotype and how MDMs can facilitate the robust interpretation of genomic variation.

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| 09:00 | Next-generation phenotyping and the link between genotype and phenotype – LGMDE threads  
   **Prof David FitzPatrick**  
   **MRC Human Genetics Unit, University of Edinburgh, UK** |
| 09:20 | Aggregating data to build knowledge  
   **Dr Helen Firth**  
   **Cambridge University Hospitals, UK** |
| 09:40 | GEL data and portals  
   **Dr Richard Scott**  
   **Rare Disease Lead, Genomics England, UK** |
| 10:00 | MDM working for the Genomic Medicine Service: Lightning talks from each of the hubs (up to 7 talks) |

#### Morning coffee

#### Session 11: Future frontiers – beyond single gene variants in the coding sequence

In this session, you will learn about new mechanisms of disease and techniques to interrogate the non-coding space.

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| 11:15 | How mutations lead to disease – concepts of dominance and recessivity – lessons from craniosynostosis and other disorders  
   **Prof Andrew Wilkie**  
   **University of Oxford, UK** |
| 11:40 | How mutations lead to disease: the role of chromatin associated proteins  
   **Prof David FitzPatrick**  
   **MRC Human Genetics Unit, University of Edinburgh, UK** |
| 12:05 | Interrogating the non-coding space  
   **Prof Matt Hurles**  
   **Head of Human Genetics, Wellcome Sanger Institute, UK** |
| 12:30 | Splicing  
   **Prof Diana Baralle**  
   **University of Southampton, UK** |
| 12:55 | Mutations in UTR’s as a cause of disease  
   **Dr Nicola Whiffin**  
   **Research Fellow, Imperial College London, UK** |
Session 12: Future directions – therapeutics

In this session, you will hear how our increasing understanding of the genomic architecture of cancer and rare disease is driving the development of gene-directed therapies and the realisation of personalised medicine.

14:15 Rare disease and therapeutics
Prof Clara van Karnebeek
University of Amsterdam, The Netherlands

15:00 Mutational signatures in cancer therapeutics
Dr Serena Nik Zainal
University of Cambridge, UK

15:45-16:00 Course summary and wrap-up
Dr Helen Firth
Cambridge University Hospitals, UK

16:10 Coach departs to Cambridge train station and city centre