

# THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

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## A word from THE EDITOR...



Recently, whilst reviewing exam questions set for BSc Endocrinology students at Imperial College London, I was struck by the number that were related to the genetic basis of endocrine disease. It is also striking how rapid the growth of this area has been, with many of these discoveries transpiring since I was a medical student myself, and I am not that old!

The articles in this issue of *The Endocrinologist* provide a valuable update of this fast-moving field.

In this edition, Paul Brennan updates us on the '100,000 Genomes Project' and Anna Gluck discusses the challenges of researching rare genetic diseases. Soo-Mi Park highlights the benefits of running a multidisciplinary endocrine genetics clinic and Jennifer Prinn describes her experience of familial genetic testing. William Drake and Morris Brown give an update on the genetic basis of primary aldosteronism. Daniel Osborn outlines hugely impactful recent advances in genome editing. Paul Newey addresses the issues of 'informed consent' and 'dealing with uncertain results' with regards to genetic testing. Sadaf Farooqi provides valuable insights into genetic factors influencing body weight and obesity, and Shivani Misra summarises important aspects of genetic testing in diabetes mellitus. Kristien Boelaert provides an overview of molecular markers in diagnosing thyroid cancer. Finally, Yalda Jamshidi looks to the future by presenting the latest developments in gene therapy.

I hope you enjoy reading this issue of *The Endocrinologist* and have a warm and delightful summer.

With best wishes

AMIR SAM

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**Dr Amir Sam (London)**  
Associate Editor:  
**Dr Helen Simpson (London)**  
Editorial Board:  
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Managing Editor: **Eilidh McGregor**  
Sub-editor: **Caroline Brewser**  
Design: **Ian Atherton, Corbicula Design**

**Society for Endocrinology**  
Starling House  
1600 Bristol Parkway North  
Bristol BS34 8YU, UK  
Tel: **01454 642200**  
Email: [info@endocrinology.org](mailto:info@endocrinology.org)  
Web: [www.endocrinology.org](http://www.endocrinology.org)  
Company Limited by Guarantee  
Registered in England No. 349408  
Registered Office as above  
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[endocrinologist@endocrinology.org](mailto:endocrinologist@endocrinology.org)

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**Become a contributor...** Contact the Editorial office at [endocrinologist@endocrinology.org](mailto:endocrinologist@endocrinology.org)

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the Autumn 2019 issue: **8 July 2019**.

Front cover image ©Shutterstock

## MAKE A DIFFERENCE TO YOUR SOCIETY

Help shape the future of endocrinology by joining the Society's Council or committees.

**31 July** is the deadline to apply or nominate a colleague for one of three vacancies on **Council** (starting November 2019).

**13 September** is the closing date for applications or nominations for places on the following **Society committees** (starting 1 January 2020):

- Corporate Liaison
- Early Career Steering Group
- Nurse
- Programme
- Public Engagement
- Science

Full details are at [www.endocrinology.org/about-us/governance/council-committee-nominations](http://www.endocrinology.org/about-us/governance/council-committee-nominations).

## ENGAGE YOUR STUDENTS WITH ENDOCRINOLOGY

Apply for the Society's Undergraduate Achievement Award to recognise and promote excellence in the study of endocrinology. Your department could receive £300 per year, for 3 years, to reward outstanding undergraduates for their endocrine-related studies. Applications close on **31 July 2019**. Find out more at [www.endocrinology.org/grants-and-awards](http://www.endocrinology.org/grants-and-awards).

## VACANCY FOR TREASURER

The Society's Treasurer, Barbara McGowan, will complete her term of office at the 2020 AGM and a Treasurer-elect will be appointed at the 2019 AGM. Nominations may be made by Council or by any two Full Members of the Society by **5 July 2019**. Find out more at [www.endocrinology.org/about-us/governance/council-committee-nominations](http://www.endocrinology.org/about-us/governance/council-committee-nominations).

## SOCIETY CALENDAR

27 June 2019  
**NATIONAL TRAINING SCHEME FOR THE USE OF RADIOIODINE IN BENIGN THYROID DISEASE**  
Birmingham, UK

11-13 November 2019  
**SfE BES 2019**  
Brighton, UK

15-17 November 2020  
**SfE BES 2020**  
Harrogate, UK

8-10 November 2021  
**SfE BES 2021**  
Glasgow, UK

[www.endocrinology.org/events](http://www.endocrinology.org/events) for full details

## SOCIETY SUPPORTED EVENTS

10 June 2019  
**RET RESEARCH COLLABORATIVE NETWORK INAUGURAL MEETING**  
London, UK

25-30 August 2019  
**SPETSES SUMMER SCHOOL - NUCLEAR RECEPTORS, EPIGENOMICS, AND DISEASE**  
Spetses, Greece

## GRANT AND PRIZE DEADLINES

12 June 2019  
**REGIONAL CLINICAL CASES MEETING GRANT**

8 July 2019  
**ENDOCRINE NURSE AWARD**

8 July 2019  
**MEDAL NOMINATIONS**

31 July 2019  
**UNDERGRADUATE ACHIEVEMENT AWARD**

14 August 2019  
**TRAVEL GRANTS**

28 August 2019  
**SfE BES REGISTRATION GRANTS**

25 September 2019  
**PUBLIC ENGAGEMENT GRANTS**

30 October 2019  
**PRACTICAL SKILLS GRANTS**

20 November 2019  
**EARLY CAREER GRANTS**

20 November 2019  
**EQUIPMENT GRANTS**

20 November 2019  
**ENDOCRINE NURSE GRANTS**

[www.endocrinology.org/grants-and-awards](http://www.endocrinology.org/grants-and-awards) for full details of all Society grants and prizes

## NEW ADVICE FOR ACUTE HYPOCALCAEMIA

An addendum updates the dose advice on the Society's clinical guidance for emergency management of acute hypocalcaemia in adults. You can read it at [www.endocrinology.org/clinical-practice/clinical-guidelines](http://www.endocrinology.org/clinical-practice/clinical-guidelines).

## HELP INSPIRE FUTURE ENDOCRINOLOGISTS

Apply for a Public Engagement Grant today! Funding is available for worksheets, factsheets or quizzes, short video clips or podcasts, or anything else you can think of. You could create learning resources for our You and Your Hormones website, or help schoolteachers and pupils learn about endocrinology. Visit [www.endocrinology.org/grants-and-awards/grants/public-engagement-grant](http://www.endocrinology.org/grants-and-awards/grants/public-engagement-grant) to find out more. Apply before **25 September 2019**.

## THE FUTURE OF ENDOCRINOLOGY AND DIABETES TRAINING

The Society has worked with Association of British Clinical Diabetologists to produce a joint position statement with recommendations for specialty training in endocrinology and diabetes. See [www.endocrinology.org/clinical-practice/society-position-statements](http://www.endocrinology.org/clinical-practice/society-position-statements).

## OUR BEST ENDOCRINE ACADEMY YET!

Thank you to all who were involved in Endocrine Academy 2019 in Birmingham. The event was a sell-out success, and we hope all delegates enjoyed this popular, essential training and networking event. Don't miss out: register early when next year's dates are announced.

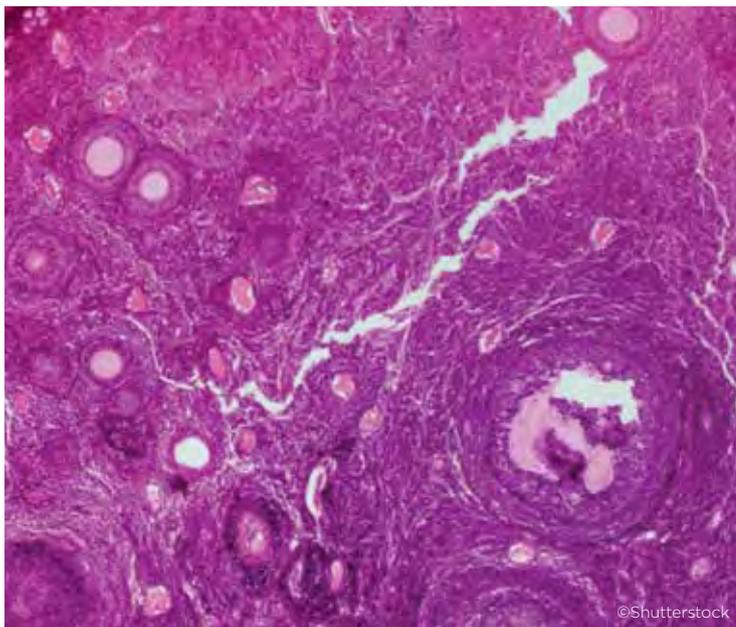


## SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the members' area on the Society home page, [www.endocrinology.org](http://www.endocrinology.org). *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access and free to all.



## JOURNAL OF ENDOCRINOLOGY



### Inhibitors of apoptosis protect the ovarian reserve from cyclophosphamide

As we know one of the successes of modern medicine is that 2.5 million people now live with and beyond cancer. Cancer therapy may result in primary ovarian insufficiency in girls and premenopausal women. Loss of ovarian follicles within the ovarian reserve leads to ovarian endocrine dysfunction and impaired fertility.

Cyclophosphamide (CPA) is a gonadotoxic agent that destroys ovarian cells by crosslinking DNA. Luan *et al.* sought to precisely map the mechanism by which the ovarian reserve is depleted by CPA. They described how the active metabolite of CPA, 1  $\mu$ M 4-hydroxyperoxycyclophosphamide (4-HC), specifically depletes primordial follicles without affecting primary and secondary follicles in three independent murine strains (CD-1, C57BL/6J and BALB/c) *in vivo*, and demonstrated that phospho-AKT (p-AKT) and cleaved PARP (cPARP) are present in primordial oocytes 3 days after CPA injection, consistent with the role of these markers as part of the apoptotic cascade.

Additionally, treatment of animals with specific inhibitors of apoptotic pathway components, ETP46464 and CHK2, blocked 4-HC-induced DNA damage *in vitro*. These data suggest that CPA targets primordial germ cells in the ovarian reserve by stimulating apoptosis pathways.

This is an exciting paper as it suggests that adjuvant therapies to protect primordial germ cells from the off-target effects of CPA may reduce the risk of POI, and brings hope for future fertility to many girls and women.

Read the full article in *Journal of Endocrinology* **240** 243–256

## JOURNAL OF MOLECULAR ENDOCRINOLOGY

### PEG10 is associated with treatment-induced neuroendocrine prostate cancer

It has been suggested that the placental gene *PEG10* may have a role in the neuroendocrine (NE) differentiation of advanced prostate adenocarcinoma following androgen receptor (AR) axis-directed therapy.

Kim *et al.* used a unique model of enzalutamide resistance (ENZR) and neuroendocrine differentiation to study *PEG10*/AR interplay in enzalutamide treatment-resistant cell lines 42D<sup>ENZR</sup> and 42F<sup>ENZR</sup> compared with LNCaP and castration-resistant 16D<sup>CRPC</sup> cells.

ENZR cell lines with positive terminal neuroendocrine marker status displayed higher baseline expression of *PEG10* compared with LNCaP and 16D<sup>CRPC</sup>. Antagonism of AR activity increased *PEG10* expression, followed by an increase in terminal neuroendocrine markers. Conversely, stimulating AR activity via androgen supplementation reversed *PEG10*

and neuroendocrine marker expression in a time- and dose-dependent manner.

These results were supported by human data showing that *PEG10* expression is highest in neuroendocrine prostate cancer (NEPC) and that an AR-dependent gene (for prostate-specific antigen) is negatively correlated with *PEG10* in adenocarcinoma. Furthermore, ChIP assay confirmed binding of activated AR to the *PEG10* enhancer, decreasing *PEG10* expression.

While *PEG10* did not drive NEPC, its knockdown reduced neuroendocrine markers in the cell lines. Moreover, *PEG10* knockdown *in vitro* and *in vivo* attenuated tumour growth. Overall, these observations indicate that *PEG10* is an AR-repressed gene which modulates neuroendocrine markers in ENZR cells, and that targeting *PEG10* in advanced prostate cancer with neuroendocrine features may yield therapeutic potential.

Read the full article in *Journal of Molecular Endocrinology* **63** 39–49

## ENDOCRINE-RELATED CANCER

### ER $\alpha$ regulates syndecan-1 in human breast cancer

Breast cancer is the primary cause of cancer-related mortality among women. Patients who express the oestrogen receptor (ER), which mediates the tumorigenic effects of oestrogens, respond to antihormonal therapy. Loss of ER expression or acquired resistance to oestradiol is associated with aggressive malignant phenotypes, which lead to relapse. These breast cancer subtypes overexpress syndecan-1 (*SDC1*), a transmembrane heparan sulfate proteoglycan that mediates angiogenesis, as well as the proliferation and invasiveness of cancer cells.

Fleurot *et al.* have shown that activation of ER $\alpha$  by oestrogens induces down-regulation of *SDC1* expression in ER-positive MCF7 cells, but not in T47D cells. Loss of ER $\alpha$  expression, induced by RNA interference or a selective ER down-regulator, led to subsequent *SDC1* overexpression. Oestradiol-dependent down-regulation of *SDC1* expression required *de novo* protein synthesis, and was

antagonised by treatment with BAY 11-7085, an irreversible inhibitor of I $\kappa$ B $\alpha$  phosphorylation, which inhibits the activation of NF $\kappa$ B. Down-regulation of *SDC1* expression required ER $\alpha$  and activation of IKK, but was independent of downstream transcriptional regulators of NF $\kappa$ B. BAY 11-7085 prevented oestradiol-mediated phosphorylation of ER $\alpha$  on Ser118, increasing its proteasomal degradation, suggesting that IKK stabilised oestradiol-activated ER $\alpha$ , leading to subsequent down-regulation of *SDC1* expression.

Results showed that sustained ER signalling inhibits *SDC1* expression. Such antagonism elucidates the inverse correlation between *SDC1* and ER expression in ER-positive breast cancer, as well as the overexpression of *SDC1* in hormone receptor-negative breast cancer subtypes with the most aggressive phenotypes. These results identify *SDC1* as an attractive therapeutic target for breast cancer, as well as for other endocrine-associated cancers.

Read the full article in *Endocrine-Related Cancer* doi:10.1530/ERC-18-0285

## CLINICAL ENDOCRINOLOGY

### Adolescent use of combined hormonal contraception and peak bone mineral density

This is an interesting meta-analysis suggesting that combined hormonal contraception (CHC) use in adolescents is associated with a lower peak bone mineral density (BMD) at the lumbar spine if used between ages 12 and 19.

CHC use is common and is also used in young girls who have ovarian insufficiency of any cause. We know that adolescence is a time for peak accrual of bone density. Goshtasebi *et al.* performed a 12-month LS meta-analysis with eight paired comparisons in 1535 adolescents showed a weighted mean BMD difference of  $-0.02$  in CHC-exposed adolescents ( $P=0.04$ ) and the 24-month

LS meta-analysis with five paired comparisons in 885 adolescents showed a highly significant weighted mean BMD difference of  $-0.02$  in CHC-exposed adolescents ( $P=0.0006$ ). Adjustments for age and/or race, BMI and baseline BMD were made in four out of nine studies.

Not all studies described smoking, calcium intakes, alcohol consumption and exercise levels. This was not a randomised placebo-controlled trial, and describes an association; however, the data are highly statistically significant and we may need to pause for thought when considering CHC use in adolescents who have yet to accrue their peak bone mass.

Read the full article in *Clinical Endocrinology* **90** 517–524

## ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

### Hypertension in pregnancy due to DOC-secreting tumour

Marques and colleagues report an unusual cause of hypertension detected in pregnancy. An incidental adrenal mass was detected during obstetric ultrasound in a woman with a history of pre-eclampsia, hypertension requiring three agents, and also hypokalaemia. She did not have features of Cushing's syndrome and had aldosterone and renin levels that were low rather than high.

The patient was found to have grossly elevated levels of 11-deoxycorticosterone (DOC), a mineralocorticoid precursor. Magnetic resonance imaging demonstrated a 12-cm complex cystic adrenal mass. Treatment with

antihypertensives (labetalol, doxazosin, diltiazem) continued until the post-partum period, at which point the woman underwent surgical resection of what was found to be an adrenocortical neoplasm. Her hypertension and hypokalaemia resolved post-operatively.

The authors discuss the differential diagnosis of a picture of mineralocorticoid excess, as well as what is currently known about DOC-producing adrenal tumours.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* doi: 10.1530/EDM-18-0164

## ENDOCRINE CONNECTIONS

### Are higher urinary cortisol levels associated with increased cardiovascular risk?

There are conflicting data on whether variations in physiological cortisol levels are associated with cardiovascular risk, and it can be difficult to compare results from previous studies because of varying sample size, techniques for assessing cardiovascular risk and failure to adequately account for environmental factors.

To address these issues, Haas *et al.* used a large sample size, selected the Framingham risk score to compute cardiovascular risk and performed the study in a highly controlled setting. They aimed to determine whether higher cortisol levels were associated with increased cardiovascular risk and whether caveolin-1 (rs926198) risk allele carriers had increased cardiovascular risk.

This was a cross-sectional study of 574 non-diabetic individuals who completed a common protocol. Data collection included fasting blood samples, blood

pressure measurements and 24-h urine free-cortisol collection. Of these participants, 517 also completed caveolin-1 genotyping. Subjects were classified as belonging to either the low-mode or high-mode urine free-cortisol groups, based on the bimodal distribution of urine free-cortisol.

In multivariate analysis, Framingham risk score was statistically higher in the high-mode cortisol group ( $10.22 \pm 0.43$ ; mean  $\pm$  SEM) compared with the low-mode cortisol group ( $7.73 \pm 0.34$ ;  $P < 0.001$ ). Framingham risk score was also statistically higher in the caveolin-1 risk allele carriers ( $8.91 \pm 0.37$ ) compared with caveolin-1 non-risk allele carriers ( $7.59 \pm 0.48$ ;  $P = 0.034$ ).

These data still do not prove causation and call into question any suggested intervention: should we be aiming to lower urine-free cortisol, or should we heed advice to watch our weight, BP and exercise?

Read the full article in *Endocrine Connections* doi:10.1530/EC-19-0182

## ENDOCRINE HIGHLIGHTS

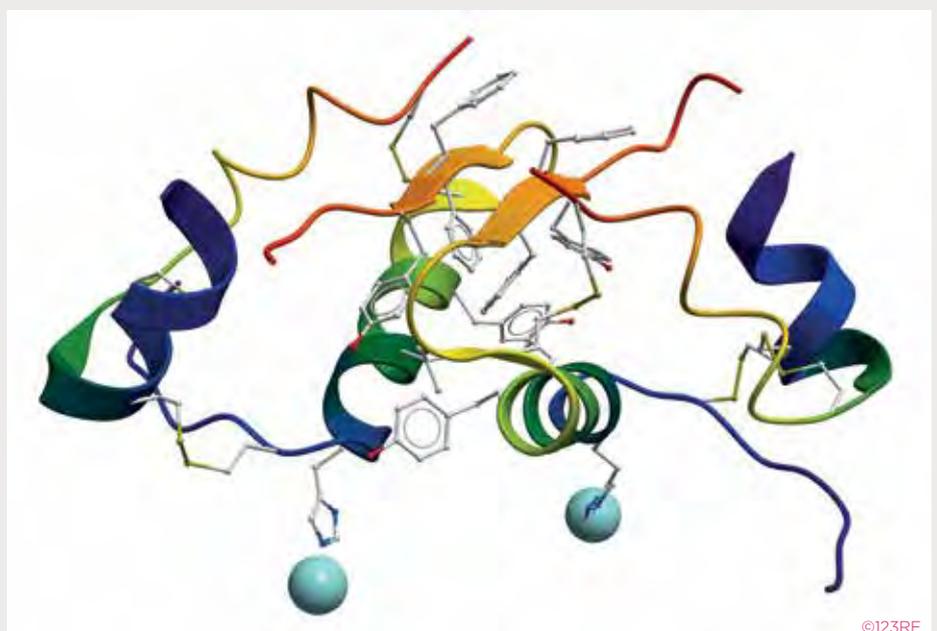
A summary of papers from around the endocrine community that have got you talking.

### Insulin entrains circadian rhythms with feeding times

In the field of chronobiology, it has been understood for some time that food intake is an important timing cue (a 'zeitgeber') for the circadian clock. This has led to hypotheses about how the deleterious effects of mistimed meals, or erratic eating patterns (during shift work, for example), might come about. However, the mechanism by which feeding entrains the clock has proved elusive.

Now, using mouse and *in vitro* studies, Crosby *et al.* have shown the importance of insulin and the insulin signalling pathway for resetting the clock. Insulin signalling leads to the induction of PERIOD proteins, which are an important component of the negative feedback loop of the molecular clock. Interestingly, the suprachiasmatic nucleus of the hypothalamus, which receives input from the retinohypothalamic tract and thus co-ordinates organismal rhythms with the light–darkness cycle, was found to be more resistant to the effects of insulin than peripheral tissues. For mice kept in constant darkness, however, delivery of 'mistimed' insulin had significant enough effects on the clock to disrupt patterns of activity onset, highlighting the importance of insulin signalling as a zeitgeber.

Read the full article in *Cell* **177** 896–909



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# THE 100,000 GENOMES PROJECT

WRITTEN BY PAUL BRENNAN



I have seen the future. It consists of six billion nucleotides (a tiny bit less if you're genetically male). Whole genome sequencing (WGS), once a 'holy grail', will be routine for many NHS patients in England from 2019.

In a recent clinic, I met an old friend called Robert. I've seen him on and off for a decade since he was transferred to me by a colleague who had made a clinical diagnosis of Shprintzen–Goldberg syndrome (SGS) in the days before genetic testing was possible. SGS is a rare genetic condition that shares some features with Marfan syndrome but, in particular, includes a relatively small head and mild learning problems. Mutations in the *SKI* gene were first described in people with SGS in 2012, although Robert's *SKI* genes were tested and found to be normal. Robert lived without a diagnosis until 2pm on 13 March 2019, when I was able to end 31 years of diagnostic uncertainty.

How? He and his parents had taken part in the 100,000 Genomes Project. We were able to analyse far more genes than previously possible and there was the answer: Robert is a compound heterozygote for two different mutations in a gene called *ASPM*. He has autosomal recessive primary microcephaly type 5. End of story. Or is it?

## POLITICS AND AMBITION

The 100,000 Genomes Project in England was the brainchild of politicians determined to make the NHS in England the first healthcare service in the world to use WGS as a routine first-line diagnostic test for people with undiagnosed rare diseases and individuals with cancer. The scale of the ambition was staggering: over a period of 4 years or so,

70,000 NHS patients would undergo WGS (people with cancer undergo WGS in their tumour DNA *and* their germ line, bringing the total number of genomes to 100,000).

By 29 March 2019, when the project officially ended, over 100,000 whole genomes had been sequenced in 85,000 NHS patients. At the time of writing, this was the largest number of genome sequences *ever* undertaken in a healthcare setting anywhere in the world.

## PRACTICALITIES

People with rare inherited diseases were eligible for WGS if they had specific disorders (see Table 1 for the eligible endocrine disorders) and had already undergone 'standard' genetic testing, if available. Priority was given to multi-case families or 'trios' (affected child plus both unaffected parents). Consenting to WGS was not trivial: each participant was asked to sign a five-page form with several options relating to the extent of analysis and use of the sample for research (Table 2).

*'...when the project officially ended, over 100,000 whole genomes had been sequenced in 85,000 NHS patients ... the largest number of genome sequences ever in a healthcare setting anywhere in the world.'*

**Table 1.** 100,000 Genomes Project: eligible rare endocrine disease diagnoses

- Congenital adrenal hyperplasia
- Familial/sporadic hypoparathyroidism
- Disorders of sex development
- Early-onset familial ovarian failure
- Unexplained intrauterine growth restriction
- Idiopathic hypogonadotrophic hypogonadism
- Early-onset severe syndromic or non-syndromic obesity
- Familial early-onset non-insulin-dependent diabetes
- Hyperinsulinism
- Neonatal diabetes
- Diabetes with additional phenotypes suggestive of a monogenic aetiology
- Insulin resistance (including lipodystrophy)
- Multi-organ autoimmune diabetes
- Congenital hypothyroidism
- Resistance to thyroid hormone
- Multiple endocrine tumours
- Pheochromocytoma/paraganglioma
- Parathyroid carcinoma
- Familial non-medullary thyroid cancer

See [www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project](http://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project) for a list of all of the eligible diseases.

High quality germline DNA, extracted from blood, was shipped to a national biobank, then on to a purpose-built genome sequencing facility on the Wellcome Genome Campus in Hinxton (Cambridge, UK) for WGS, after which *analysis* was restricted to a panel of carefully selected genes, driven by the reported phenotype, as well as optional 'secondary findings' gene panels. Gene panels were defined by a purpose-designed open-access tool called PanelApp.<sup>1</sup>

People with most solid or haematological cancers were also eligible for WGS in both their tumour and their germ line. Here, however, the project hit two early problems. The first was formalin: this toxic chemical has been used for decades and, although it preserves tissue for histology, it also renders DNA unsuitable for WGS. Operating theatres across England faced (and many still face) the challenge of removing formalin and sending tumour tissue fresh to pathology departments for selection of tissue suitable for DNA extraction. Sounds easy, doesn't it? It isn't, believe me.

Haemato-oncologists also faced a challenge: we usually use blood samples to extract germline DNA for WGS, but what if the patient has leukaemia? Alternative sources of germline

**Table 2.** Consent options for whole genome sequencing (WGS)

- Collection and use of samples for WGS
- Collection and use of health data
- Analysis of genes relevant to the patient's disease (defined by PanelApp)
- Analysis of genes associated with 'secondary findings' (genes which may cause serious or life-threatening diseases e.g. *BRCA1/2*, Lynch syndrome, familial hypercholesterolaemia; these now also include pharmacogenomics variants that may predict adverse response to drugs)
- Analysis of genes associated with 'reproductive findings' (carrier status for serious or life-threatening autosomal recessive or X-linked disorders that might affect the participant's child(ren) e.g. cystic fibrosis)
- Access to genome and clinical data by researchers and/or commercial companies

DNA are needed: skin biopsies, fluorescence-activated cell sorter-enriched non-tumour leucocytes or saliva, for example. This challenge is still being addressed, but it will be solved.

## OUTCOMES

At present, the routine 100,000 Genomes Project data pipeline effectively asks 'is there a variant of interest in these specific genes?'. This is not the same as whole genome analysis, in which the question is 'is there a variant of interest in this entire genome?'. Cancer data analysis is more complex and requires a broader approach to detect large and small scale genomic rearrangements. Using these current approaches, just over 20% of patients with rare diseases get a diagnosis (on average: the hit-rate is higher for some disorders and lower for others). A greater proportion of cancer patients are found to have a clinically actionable variant that links to a therapy or trial opportunity.

*'...accurate, complete phenotyping is vital when it comes to interpreting VUSs. It turns out that diagnostic skills are just as important in the genomic era as ever before.'*

The challenge of data analysis on this scale is truly staggering and, although this 'first-pass' analysis might seem relatively restricted, we can expect wider analyses as the data are re-examined periodically as part of the legacy activities of the 100,000 Genomes Project.<sup>2</sup>

Further analysis of genome data can also be undertaken by researchers working as part of disease-specific GeCIPs (Genomics Clinical Interpretation Partnerships), for example the Endocrine and Metabolism GeCIP.<sup>3</sup> These are groups of interested clinicians and academics who have agreed to collaborate on specific projects using the clinical and genome data resource compiled during the 100,000 Genomes Project.

Throughout 2019 we will see the return of thousands of results from Genomics England to the NHS Genomic Medicine Centres. Many centres have already developed a great deal of experience in validating such results and providing clinicians with clinical-grade reports for their clinics.

## UNCERTAINTY

One particular challenge is a term you will all need to familiarise yourselves with: 'variants of uncertain significance' (VUS or VOUS). At present, our understanding of the genome is relatively basic. We simply haven't got to grips with the full extent of normal genome sequence variation. It's a bit like the biggest challenge at medical school: to learn what is normal. It is not uncommon – at present – for DNA sequencing to identify a variant in our DNA that cannot be classified as either 'normal' or 'pathogenic' (the term 'mutation' is falling out of use<sup>4</sup>). We can expect VUSs to be commonplace for many decades to come, and we will see the rapid development of 'genomics multidisciplinary teams' in the NHS to support clinicians faced with a VUS.

One thing has become clear already: accurate, complete phenotyping is vital when it comes to interpreting VUSs. It turns out that diagnostic skills are just as important in the genomic era as ever before.

*'We are Generation Genome.'*

## THE FUTURE

This year, the NHS in England will launch the NHS Genomic Medicine Service. Existing DNA diagnostics provision is being reorganised to create seven Genomic Laboratory Hubs, supported by seven Genomic Medicine Centres, providing comprehensive DNA analysis for both rare diseases and cancer. For the first time, clinicians across the NHS will have direct access to tests – including WGS for some diseases – which may for years have been the sole domain of clinical genetics services. This will not be a single event, but a process that will take time.

We are Generation Genome.<sup>5</sup> Genomics is no longer locked in its ivory tower. Let's work together to realise its full potential for our patients. It's a big challenge, for sure, but we're the first health service in the human universe to do it at such scale and pace, so let's get it right.

## PAUL BRENNAN

Consultant in Clinical Genetics, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne

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# THE CHALLENGES OF RESEARCHING RARE GENETIC DISEASES



WRITTEN BY ANNA GLUCK



As a young researcher, I find studying rare genetic conditions both rewarding and challenging. In the EU, a disease is defined as rare if it affects fewer than one in 2000 people,<sup>1</sup> with the majority of cases thought to be of genetic origin.

The most prevalent monogenetic disorder is cystic fibrosis. It is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and affects mainly the lungs, but also other organs, such as the pancreas, liver, kidneys and intestines. The condition affects one in 3000 newborns,<sup>2</sup> which equates to 226 new patients in England and Wales every year.<sup>3</sup> This life-threatening condition is common enough and severe enough for many countries to have implemented screening in maternity wards.

Most conditions, however, are much rarer than that. Personally, I work on disorders related to calcium homeostasis, and here prevalence as low as one in 13,000 individuals<sup>4</sup> has been reported.

## THE RESEARCH CONUNDRUM

Even though the individual conditions are rare, the chance of having a rare disease is nevertheless quite high. According to estimates by the National Institutes for Health Research (NIHR), rare diseases could affect as many as 10% of the population. Here, we have a conundrum: on the one hand, we want to help the millions of patients living with these rare conditions; on the other hand, it is not lucrative for funding bodies and pharmaceutical companies to invest resources in this area, because the cost of developing a treatment for a rare disease is no cheaper than for a prevalent one.

This problem has partly been addressed by the Orphan Drug Act 1983, offering financial and regulatory incentives to companies developing and selling such treatments. However, the return on investment will still be much lower than for common conditions.

## UNDERSTANDING THE UNDERLYING BIOLOGY

Even where there is the incentive to find novel treatments, we first need to understand the underlying biology. The publication of the human genome in 2003 transformed the field of genetic research. However, investigation of rare genetic diseases has proved especially difficult. Traditionally, it is based on family studies. In theory, the recipe is simple: take a kindred with an inherited disease, identify mutations that are unique to affected family members as opposed to unaffected ones and show that there is a functional change in a suitable *in vitro* system.

In practice, this requires access to an entire family's medical history and patient samples, which in the modern world often involves co-ordination between several hospitals in different parts of the country. Within any single family, thousands of genetic mutations are shared. Even when comparing multiple affected versus unaffected family members, we still find ourselves with dozens (or if we are unlucky, hundreds) of candidate genes, each of which has to be painstakingly tested. We therefore normally require a large number of patients from multiple families for the study. With a rare condition, it can be impossible to obtain sufficient samples to achieve a scientifically rigorous conclusion.

A more modern approach is to use large scale sequencing databases that link genetic variants to phenotype data (such as the UK Biobank). However, genome-wide association studies (GWAS) have limitations for rare diseases, because screening thousands of genes in very few patients is likely to yield false-positive results. To obtain statistical power, GWAS rely on large sample sizes, which are only available for common diseases. Additionally, these databases are often retrospective observations rather than prospective studies, which means that data and diagnosis can be missing and/or unreliable, and family history is often not available.

## OPPORTUNITIES FOR TREATMENT

Despite these challenges, there have been success stories with direct patient benefit. One of the big opportunities for the treatment of rare diseases is drug repurposing, which is a lot more cost-effective than developing a drug from scratch. In some cases, existing indications can be extended to rare diseases. For example, our research group identified a novel *GNA11* mutation in a patient with familial hypocalcaemic hypercalcaemia type 2 and showed impairment of the calcium-sensing-receptor (CaSR) signalling pathway *in vitro*. In collaboration with Helsinki University Hospital, Finland, the patient was treated with cinacalcet, a positive allosteric modulator of CaSR, which is approved for the treatment of secondary hyperparathyroidism, caused by end-stage renal disease. As a result, the patient became normocalcaemic.

Another interesting approach is to make use of the many compounds that have been shown to be safe for use in humans, but failed in clinical trials because they were not effective enough for the indication for which they were tested. For example, the calcilytic ronacaleret failed in a phase II study because of lack of efficacy in postmenopausal women with osteoporosis. It has recently been shown to rectify impaired glucose tolerance in a mouse model for inherited hyperglycaemia, making it a potential candidate for the treatment of genetic forms of diabetes.

Gene therapy is currently a last resort treatment for certain cancer types. Looking to the future, it is certainly a promising therapeutic approach for genetic diseases. However, germline mutations occur in every single cell of our body and targeting therapies to specific tissues will be a challenge.

In conclusion, researching rare diseases is crucial for millions of patients worldwide. Without the incentives for pharmaceutical companies to investigate treatments, it falls mainly to universities and research labs to identify the genetic mutations responsible, and to propose new treatments. This not only benefits the patients, but also advances our understanding of the underlying biology. Moreover, with an increasing number of companies offering DNA self-testing, we need to educate and inform the public about the work we do to differentiate between benign polymorphisms and disease-causing mutations.

## ANNA GLUCK

PhD Student, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford

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# MULTIDISCIPLINARY ENDOCRINE GENETICS CLINIC: THE BENEFITS AND CHALLENGES

WRITTEN BY SOO-MI PARK



The era of genomic medicine has been transforming the clinical care of patients in mainstream medicine. Next generation sequencing (NGS) on whole exome platforms is soon to be phased into whole genome platforms, now that the piloting of the 100,000 Genomes Project ([www.genomicsengland.co.uk](http://www.genomicsengland.co.uk)) is coming to an end. It has enabled more accessible genetic tests than ever.

The genetic testing landscape has changed dramatically in the last decade: from single gene tests, moving on to panel gene tests and recently on to agnostic trio whole exome, and now genome, sequencing. This is a time of unprecedented increase in knowledge of the genetic basis of disease against a background of rapidly changing technology, and has been translated into the highest diagnostic rate for hereditary disorders in medical history. It is therefore not surprising that there is an increasing demand for, and expectation of, genetic services.

Many patients seen in endocrinology and diabetes clinics are at risk of having a monogenic basis to their disorder; from rare neuroendocrine tumours such as pheochromocytomas and paragangliomas, and multiglandular disease, to the more common disorder of primary hyperparathyroidism. Maturity-onset diabetes of the young (MODY) and mitochondrial diabetes are also considerations in those with familial diabetes. The practising endocrinologist therefore needs to carefully consider whether a genetic basis is worth exploring by taking a careful family history in the first instance. Diagnosing a hereditary disorder not only benefits the patient, but also their wider family.

## KEY QUESTIONS

Endocrinologists may be knowledgeable about many of the familial endocrine disorders (after all, they are the 'bread and butter' of MRCP exams!). However, most endocrinologists may not be familiar with arranging genetic tests, interpreting the reported variants, the need to arrange cascade family screening, providing advice about recurrence risk and reproductive options. Key questions are:

- Is the test a diagnostic test?
- Is it a predictive test where there is a known familial disorder and a known familial pathogenic variant?
- Are they seeking a predictive test in a child for an adult-onset disorder, for which there are clear guidelines from the British Society for Genetic Medicine ([www.bsgm.org.uk](http://www.bsgm.org.uk))?
- Are they seeking a carrier test for an autosomal recessive disorder or an X-linked disorder?
- Are they familiar with the availability of single genes and multiple gene panels (by disorder or an all-encompassing inherited cancer exome panel)?
- Are they aware of the limitations of NGS tests, such as poor optimisation for the detection of dosage changes (small deletions or duplications), and therefore the need to request additional tests such as multiplex ligation-dependent probe amplification (MLPA) analysis?
- Do they know of the timescale for results (on average, 4 months for NGS panel testing, 2 months for single gene testing, 2–4 weeks for predictive genetic testing, 1–2 weeks for urgent prenatal testing)?
- Are they experienced in obtaining formal written consent (standard forms are available from genetics services) for genetic testing, which covers aspects such as sharing results with the rest of the family and preparing the patient for the possibility of unexpected results? This includes the possibility of finding a variant of uncertain significance

(VUS), usually a novel missense variant in a gene where the pathogenic changes are commonly loss-of-function variants. Interpretation of such variants requires expertise and additional training.

Once a genetic diagnosis is confirmed, most affected individuals are naturally concerned and anxious about the risk to their immediate family and seek advice about risk to their relatives, their future children and how to access genetic testing and screening for disorders. Those of reproductive age do not wish to pass on their disorder to their children and therefore seek information about the options available.

## MULTIDISCIPLINARY CLINICS

A joint clinic with a clinical geneticist appears sensible, in which the expertise of both specialties can be harnessed for optimum patient management. Clinical genetics services in the UK are offered regionally in a 'hub and spoke' model. Specialist genetics multidisciplinary clinics are often held in regional tertiary teaching hospitals, which draw patients from the whole region served and often quite a way beyond, depending on the geography covered by the referring specialist service, e.g. head and neck paragangliomas referred by a national skull base surgical service. It is standard practice for a clinical geneticist to draw up a family history covering three to four generations. This can be useful for:

- providing detailed information about affected members
- seeking confirmation of the disorder and obtaining a mutation report if available
- identifying the presence of any consanguinity
- identifying at-risk relatives
- determining the likely inheritance pattern
- ensuring that confidentiality is strictly observed between members of the same extended family, except where specific consent to share information is obtained.

The geneticist can inform the patient about the diagnosis or diagnoses in consideration, their inheritance pattern(s) and therefore the potential risks to their relatives, the implications of having a diagnostic or a predictive genetic test, and the implications for insurance policies of the latter test, and also advise when childhood predictive testing is appropriate.

Various reproductive options can also be discussed for couples where any future children are at high risk. These include:

- non-invasive prenatal diagnosis for paternally inherited autosomal dominant disorders or autosomal recessive disorders where the couple are confirmed carriers, or sexing for X-linked disorders
- invasive prenatal diagnosis by chorionic villus sampling or amniocentesis
- pre-implantation genetic diagnosis for disorders approved by the Human Fertilisation and Embryology Authority ([www.hfea.gov.uk](http://www.hfea.gov.uk)).

The genetic test is then arranged after written consent is obtained, where the option of sharing their results with family members is included as an integral part (so that future cascade family testing can take place smoothly without breaking confidentiality). The possibility of unexpected results, including a VUS, is discussed in the consent process, as well as anonymous use of the test results to improve healthcare within the NHS (useful for valuable NHS audit projects). If a genetic disorder is confirmed, then the genetics service is well accustomed to facilitating family cascade testing with the generation of an open 'To Whom It May Concern' letter that can be passed to the at-risk family members, thereby assisting with GP referrals for these relatives.

## THE FUTURE

The challenge with genetic tests now mainly lies in interpretation of the results and any variants that are detected. Life would certainly be easier

for all practising clinicians who regularly request genetic tests if we had long-established and detailed databases of both pathogenic variants for known disorders and variants present in the general population presumed to be harmless or of low penetrance. Databases for both do exist (ClinVar, [www.ncbi.nlm.nih.gov/clinvar](http://www.ncbi.nlm.nih.gov/clinvar); HGMD, [www.hgmd.cf.ac.uk](http://www.hgmd.cf.ac.uk); DECIPHER, <https://decipher.sanger.ac.uk>; gnomAD, <https://gnomad.broadinstitute.org>) and can prove helpful in many cases, but more information still needs to be gathered and compiled for this process to be facilitated. The UK has led the world on nationally co-ordinated whole exome and genome sequencing research studies (e.g. DDD study, <https://decipher.sanger.ac.uk/ddd>, and the 100,000 Genomes Project) through our integrated NHS services, and results from these studies are generating much-needed information for the genomic databases, which will help ease the burden of interpreting variants in the future.

NHS England, through its NHS Genomic Medicine Service initiative ([www.england.nhs.uk/genomics/nhs-genomic-med-service](http://www.england.nhs.uk/genomics/nhs-genomic-med-service)), has recently brought about reconfiguration of genetics laboratory service

provision through commissioning seven Genomic Central Laboratory Hubs working in conjunction with the clinical genetics services, capitalising and building on the output of the 100,000 Genomes Project. This will allow access to the widest range of genetic tests to date. One of the main aims of this change is to embed genomics into mainstream medicine. Therefore, all NHS specialists will have access to, and are expected to use, genomic testing before the end of the year, on whole genome platforms where all requests are funded centrally, provided that the testing criteria are met. The requests are placed centrally but testing will be directed to the laboratory assigned to perform the relevant test. Therefore, the time has come for the endocrinologist to become genomics savvy, and a close working relationship with their local clinical geneticists becomes more pertinent than ever.

**SOO-MI PARK**  
Consultant in Medical Genetics, Addenbrooke's Treatment Centre, Cambridge University Hospitals NHS Foundation Trust

## LET'S TALK: GENETIC TESTING

WRITTEN BY JENNIFER PRINN



Jennifer Prinn considers her family's experience of genetic testing, and whether she would advise other families in similar situations to get tested.

Is genetic testing a good thing or a bad thing? For our family, I would say it has been a benefit. Let me explain why...

In 2012, I was diagnosed with multiple endocrine neoplasia (MEN) type 1, after breaking my knee in 2010 and then finally undergoing a parathyroidectomy in 2011. When we discovered I had this genetic condition we decided, because the gene is dominant, that we wouldn't have any more children. How wrong we were! Three months after my parathyroid operation, I fell pregnant (after 12 years of infertility and two previous cycles of IVF!).

While I was pregnant with my second child (my first had been born via IVF back in 2007), I underwent genetic counselling and testing. The counselling involved discussions with a geneticist, my consultant and a nurse specialist. I was also offered the opportunity to have access to a counsellor:

### THE ANXIETY

For me, knowing I had a genetic condition that had been passed down was difficult to understand. My mum passed away when I was young, presumably from a MEN-related condition, and here I was, with two children, to whom I could have passed the condition. The genetics appointment was simple, it was the wait for the results that took time as it took almost 6 months. Despite this, I would advocate genetic testing for anyone who has a strong possibility of MEN.

When my son complained of recurring pins and needles, I initially thought that this was down to growing pains. He was nearly 6 years old and,

of course, this is the right age for this to occur. Then the MEN anxiety kicked in. What if it wasn't growing pains? What if he had high calcium levels, and the pins and needles he was experiencing were a result of hyperparathyroidism? Or worse, had he developed brown tumours from exposure to high calcium for such a long time? After a long battle with my GP, who didn't really understand why I was concerned (calcium levels aren't routinely tested), they finally agreed to test my son's calcium levels. Fortunately, all was fine. But, there was still this nagging doubt in my mind. How did I know that he didn't have MEN or wasn't going to suffer the same experiences as me growing up?

### THE TESTING

Luckily, I had a consultant at King's College London who was very supportive and referred me and my husband to the genetics department at Guy's and St Thomas' Hospital in London. We were offered a further session of genetic counselling, and were required to talk about our reasons for wanting the children tested at such young ages (they were aged 5 years and 18 months at the time). Generally, testing for MEN occurs around 10 years of age, as symptoms don't tend to show before then. We explained that that I would feel much better if I knew whether the symptoms they were displaying were 'normal' childhood symptoms or MEN symptoms. If the genetics came back negative for MEN, then I could assume that the risk of anything being MEN-related was much reduced.

The appointment was long and the kids played up because they were bored. Then came the actual blood tests. The baby was easy, she sat on her dad's lap and didn't blink a eye. My son, however, being 5 at the time, decided that he didn't want a strange person sticking a needle in his hand. However, after a few minutes (which felt like hours), he reluctantly agreed. I think that testing at such a young age is valuable, as children don't remember having the blood test, and, if negative, they don't even need to know that they underwent a test. If positive, it gives them a good standing for the coming years, which will be full of blood tests and scans.

*‘So, let’s talk genetic testing. Is it worth it? For parental reassurance, where there is a high risk of transmission, then I would say 100%.’*

### THE RESULTS

The wait was agonising. Every time the phone rang I was expecting the bad news that the results were in. Two weeks before Christmas in 2012 the results came back – both kids were free from the same MEN gene that I carry. I cried, my husband cried and the girls in my office cried. Many

didn’t quite understand the huge relief that these results carried, but they knew how important it was to me.

### WAS IT WORTH IT?

So, let’s talk genetic testing. Is it worth it? For parental reassurance, where there is a high risk of transmission, then I would say 100%. You can find out whether your child has a predisposition to a disease and you can prepare yourself for all that comes with the diagnosis. Some of us are lucky, our journey with genetics stops with us, but that doesn’t stop us being grateful for the opportunity we had.

### JENNIFER PRINN

RegPharmTech, Retired Pharmacy Technician, MEN1 patient

## KEEPING UP WITH THE GENES IN PRIMARY ALDOSTERONISM

WRITTEN BY WILLIAM DRAKE AND MORRIS BROWN



Primary aldosteronism (PA or Conn’s syndrome) was previously considered a ‘niche’ area of endocrinology, limited to patients with hypertension and hypokalaemia. Clinical and molecular discoveries have propelled it into the limelight, as one of the most exciting, fast-moving areas of endocrine practice.

### PREVALENCE AND PENALTY

Prospective studies indicate that 8–13% of unselected hypertensive patients have PA, of whom only a minority have hypokalaemia.<sup>1</sup> Meta-analysis shows that the cardiometabolic penalty of PA (stroke, atrial fibrillation, ischaemic heart disease) exceeds that of essential hypertension by at least 2:1.<sup>2</sup> These data should trigger a ‘call to arms’ for development of screening strategies to detect PA, to reverse (medically or surgically) the excess morbidity. The reality is sobering; fewer than 1% of cases of PA are detected and treated.

### DETECTION AND DIAGNOSIS

No ‘real-world’ case-finding protocols (other than measuring renin and aldosterone in all hypertensive patients) are available. Endocrine Society guidelines acknowledge their inappropriateness for primary care. A recent large trial, PATHWAY-2, indicated major benefits from the addition of spironolactone in patients with resistant hypertension. This study supports the high prevalence of PA, and may add weight to calls for spironolactone to be considered earlier than step 4 in the treatment of hypertension.

### LOCALISATION AND LATERALISATION

Even at current diagnosis rates for PA, invasive investigation by adrenal vein sampling (AVS) is a major ‘bottleneck’. Only a handful of centres are able to reliably cannulate both veins – and both the end (to find unilateral PA) and the means (measurement of aldosterone/cortisol ratio) may be outdated. Fewer than half the patients with unilateral PA are cured by adrenalectomy. When 1% of the population has PA, precision medicine is required to ensure that expensive procedures lead to years of drug-free cure in a high proportion of those selected.<sup>3</sup>

Positron emission tomography–computed tomography (PET-CT) scanning has the potential to expand capacity for investigation. The most advanced PET tracer is metomidate, a methyl analogue of the anaesthetic agent etomidate. A large, prospective study, MATCH, comparing <sup>11</sup>C-metomidate PET-CT with AVS, will report in 2020. Alternative <sup>18</sup>F tracers are in development, making PET available nationally.

### GROWTHS AND GENETICS

Knowledge of the aetiopathogenesis of PA has blossomed during the past decade and is an important ‘driver’ of renewed interest and advances in practice. Most aldosterone-producing adenomas (APAs) harbour a somatic mutation of an ion channel or transporter. First recognised were mutations in the *KCNJ5* gene, a potassium channel that helps maintain cell membrane hyperpolarisation. Loss of selectivity for potassium results in sodium influx and cell membrane depolarisation, inward movement of calcium and activation of aldosterone synthesis and secretion. *KCNJ5* mutations are by far the commonest in classical Conn’s adenomas of younger women.<sup>4</sup> But their discovery revealed the paradox that these adenomas resemble cortisol-producing, rather than aldosterone-producing, cells of normal adrenal, and indeed secrete more cortisol than aldosterone. Even if their cortisol secretion is clinically insignificant, it can confound the aldosterone/cortisol ratio at AVS.

The paradox was resolved by the discovery of commoner but smaller APAs with somatic mutations in sodium or calcium ATPases (*ATP1A1*, *ATP2B3*) or calcium channels (*CACNA1D* and *CACNA1H*). These APAs resemble physiological aldosterone-producing cells, and typically elude diagnosis – at least until the onset of resistant hypertension. Their hallmark mutations, and development of PET ligands and specific antisera for aldosterone synthase,

permitted recognition of an inverse correlation between enzyme density and size of APA.<sup>5</sup> No nodule on CT/magnetic resonance imaging is too small to be an APA. Indeed, the most common sites of autonomous aldosterone production are microscopic aldosterone-producing cell clusters, 60% of which have similar mutations of *CACNA1D* to those found in APAs.<sup>6</sup> More than 40 activating mutations are now described, all in/near the Ca<sup>2+</sup> pores. Investigational inhibitors of Cav1.3, encoded by *CACNA1D*, completely suppress aldosterone secretion by adrenocortical cells, and could become the precision medicine for PA.

None of the ion channel mutations is implicated in tumour formation, nor predicts higher cure rates. However, co-existence of cortisol and aldosterone synthesis leads to secretion of unusual hybrid steroids, whose measurement as a biomarker for solitary APAs with *KCNJ5* mutation may become a valuable diagnostic and prognostic tool.<sup>7</sup> Alternatively, somatic mutations are now being found in non-ion channel genes previously associated with tumour formation, and these may identify a subset of patients with sustained clinical cure after removal of the APA. For example, *CTNNB1* mutations are found in ~5% of APAs, which allow activated  $\beta$ -catenin to enter the nucleus and re-direct cell differentiation towards its adrenogonadal origin.<sup>8</sup> The consequent high expression of luteinising hormone/human chorionic gonadotrophin receptors leads to explosive onset of PA in early pregnancy or menopause. Removal of the APA achieves sustained clinical cure, attributed to the briefness of vascular exposure to high aldosterone levels.

### RESECTION AND REDUCTION

Laparoscopic adrenalectomy is the mainstay of non-medical treatment for PA, but several factors contribute towards caution in recommending surgery: limited NHS capacity, uncertain clinical outcome, and the 1960s timewarp of resecting a whole organ as treatment for a 1-cm, benign lesion. Radiofrequency ablation (RFA) of APAs is a developing alternative. A UK

safety and feasibility study of endoscopic, transgastric RFA of left-sided APAs (FABULAS) is currently recruiting.

### CONCEPTS AND CONCLUSIONS

The PA landscape has transformed since Jerome Conn's original description in 1954,<sup>9</sup> and long held assumptions may shortly appear naïve or oversimplistic. Is the distinction between unilateral and bilateral PA truly binary? Do we 'cure' patients by surgery or merely 'debulk' their disease? For anyone with a developing clinical and/or academic interest in PA – your timing is impeccable.

#### WILLIAM DRAKE

Professor of Clinical Endocrinology, Barts and the London School of Medicine

#### MORRIS BROWN

Professor of Endocrine Hypertension, Barts and the London School of Medicine

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## CRAFTING THE IMPERFECT GENOME

WRITTEN BY DANIEL OSBORN



Recent advances in genome editing are revolutionising the way we tackle big scientific questions. Tools have been developed that act like tiny 'molecular scissors', causing targeted genomic cuts in DNA. By exploiting cells' innate DNA repair mechanisms, scientists can repair aberrant genes or modify the genetic code to their liking. With these tools, we can correct pathogenic mutations, model human genetic disease in cells and animal systems, modify key organisms for biotechnology and agriculture, and potentially eradicate hereditary monogenic disease.

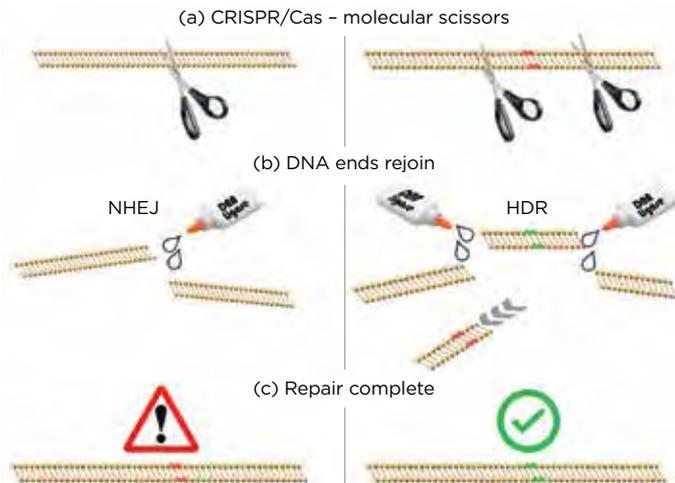
### RESTORING DNA BREAKS

A number of different methods exist to cause genomic cuts; however, repair mechanisms remain the same. DNA breaks can occur naturally through intracellular nucleases/reactive oxygen species or externally by ionising radiation/ultraviolet light. If left unrepaired, the damage will lead to cell death. Luckily, the cell has developed natural processes to fix breaks. Repair can follow one of two paths: non-homologous end joining (NHEJ) or homology-directed repair (HDR).<sup>1</sup>

NHEJ is a fast simple method, generally favoured when broken ends are compatible.<sup>2</sup> Here, specific proteins guide the alignment of the broken ends,

joining them together using DNA ligase IV.<sup>3</sup> In the majority of cases, the correct ends rejoin. However, annealing incorrect ends or the removal of damaged nucleotides can lead to chromosomal aberrations and mutations.<sup>4</sup> Hence, NHEJ is error prone, a characteristic researchers exploit to disrupt gene function.

Conversely, HDR uses an intact copy of the gene loci to repair the broken sequence, an accurate but slow method.<sup>2</sup> After a DNA break event, pathways are activated to remove damaged nucleotides by nibbling forward and reverse DNA strands, leaving single-stranded DNA overhangs.<sup>5</sup> Subsequently, the DNA ends are coated with recombinases and co-factors,



A simplified schematic of CRISPR/Cas9-directed genome editing.

(a) CRISPR/Cas9 complex is used to target genomic DNA breaks, like 'tiny molecular scissors'. (b) DNA breaks can be repaired by either non-homologous end joining (NHEJ, left) or homology-directed repair (HDR, right). (c) NHEJ is error prone, resulting in mutations in targeted genes, permitting gene function experiments. HDR can be used to replace genetic information, mimicking or correcting pathogenic sequences (e.g. for disease modelling or personalised medicine respectively). ©D Osborn

forming homology-searching nucleoprotein filaments.<sup>6</sup> The filaments hunt for sequence homologies in sister chromatids, which guide repair.<sup>7</sup> Again, adept scientists have manipulated this process to knock-in genetic material to loci, repairing genetic variants or adding traceable tag proteins.<sup>8,9</sup> Thus, DNA repair by NHEJ or HDR forms the basis of the genome editing technique.

### MAKING PRECISE CUTS

Genomic breaks caused by natural forces are unpredictable and occur randomly. To use DNA repair mechanisms for scientific gains, researchers have developed precision DNA cutting tools. Although other genome editing tools exist (meganucleases, zinc finger nucleases and transcription activator-like effector nucleases or TALENS<sup>10</sup>), CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats with CRISPR associated protein 9) has proved to be efficient and accessible to researchers.

Coined as 'the discovery of the century', the two scientists attributed to its identification, Jennifer Doudna (Berkeley, CA, USA) and Emmanuelle Charpentier (Berlin, Germany),<sup>11</sup> have been tipped to win a Nobel Prize for their work, along with Feng Zhang (Cambridge, MA, USA), a pioneer in the use of CRISPR/Cas9 on mammalian cells.<sup>12</sup>

First discovered as a bacterial adaptive immune response to foreign invading viral DNA,<sup>13</sup> the system acts to incorporate specific portions of phage DNA into the CRISPR loci. This allows generation of homology-searching guide RNAs that bind with Cas9 endonuclease and target cuts in the viral DNA.<sup>13</sup> Synthetic guide RNAs can be designed to incorporate user-defined target sequences, and synthesised in the laboratory. Therefore, the CRISPR/Cas9 system offers a versatile and adaptive tool for generating targeted genomic breaks.

### A TOOLKIT TO TREAT DISEASE

CRISPR/Cas9 is a powerful tool and has been used to remove an erroneous exon from the dystrophin gene in mice with muscular dystrophy, resulting in restored muscle integrity and function.<sup>14-16</sup> Furthermore, proof of principle

experiments in human embryos (not destined for transplantation) used CRISPR/Cas9 and synthetic DNA template-mediated HDR to correct a mutation in *MYBPC3*, which normally causes sudden death syndrome.<sup>9</sup> Despite the obvious ethical issues surrounding the misuse of genome editing to manipulate human genetics, there are serious concerns regarding inherited off-target effects that must be resolved before reaching the clinic.

### DISSECTING THE ZEBRAFISH GENOME

Although genome editing continues to raise concerns for clinical use, it has provided immediate advances in modelling disease in animals. The zebrafish is one such organism that has benefited from improved genome editing techniques. Popular for its versatility as an *in vivo* model, the zebrafish provides rapid *ex utero* development, large numbers of embryos, ease of genetic and pharmaceutical manipulation, and over 82% disease-causing genes in common with humans.<sup>17</sup> For many years, antisense morpholino (MO) technology has been used to knockdown gene function in zebrafish, by inhibiting gene-specific translation. However, MO use has come under scrutiny in recent years.<sup>18</sup> Mutant zebrafish lines remain the 'gold standard', although generating them in the past required laborious large scale teratogen-based screens.<sup>19,20</sup> Although many mutants have been recovered for a large number of genes, many more have been missed.

The targeted nature of CRISPR/Cas9 has meant that zebrafish mutations in genes known, or suspected, to be pathogenic can be easily disrupted as a consequence of error prone NHEJ.<sup>21</sup> Although it is possible to create exact mutations that recapitulate patient variants by the addition of synthetic DNA templates for HDR, this is more challenging.<sup>22</sup> However, the technology is constantly evolving; variations in endonuclease activity are being developed to improve specificity and efficiency.<sup>23</sup>

These are exciting times. Genome editing has become commonplace in most research laboratories and the possibilities for manipulating genomic DNA for scientific advances are endless.

### DANIEL OSBORN

Senior Lecturer in Genetics, Genetics Research Centre at St George's, University of London

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# TITANIC PROGRESS IN UNCHARTED WATERS

WRITTEN BY PAUL J NEWEY



As the opportunities to undertake genomic sequencing in the clinical setting expand, physicians play an increasing role in the genetic testing process, both at the point of request and in receiving and communicating results. It is therefore paramount that doctors keep pace with all aspects of the genetic testing workflow, to provide high quality care. Here, Paul Newey considers the latest issues you can expect to encounter in the clinic.

Barely a week passes without a story hitting the headlines, heralding a major medical breakthrough only made feasible by the recent advances in DNA sequencing technology: ‘Shark DNA could help cure cancer’ ‘Skinny genes the secret to staying thin’ ‘Can your DNA tell you what to eat?’<sup>1</sup>

Inevitably, such stories raise public expectations regarding the potential utility of genetic testing to improve health, and the impact on the public consciousness is borne out by an increasing demand for direct-to-consumer testing, offered by a growing number of commercial providers.

In the UK, successive governments have displayed similar enthusiasm for genetic testing, supporting major initiatives such as Genomics England’s 100,000 Genomes Project and, more recently, announcing an ambition to map 5 million genomes over the next 5 years.<sup>2</sup>

Although such large scale sequence projects can feel far removed from day-to-day medical practice, the indications and opportunities for genetic testing in the clinical setting continue to accelerate, such that all doctors require a working knowledge of the genetic testing process that is fit for purpose. This includes having the clinical acumen to select and utilise genetic tests appropriately, as well as the necessary tools to communicate results accurately and effectively to patients and their families.

Indeed, as genetic testing moves from dedicated clinical genetics services into mainstream medical clinics, physicians need to be aware of the many challenges associated with contemporary testing. Two such areas include ‘What constitutes informed consent?’ and ‘What should we do when we receive uncertain test results?’

## INFORMED CONSENT: IS GENETIC TESTING SPECIAL?

In the minds of both the medical profession and the general public, genomic data carry a special status. As a consequence, genetic testing has typically involved the provision of genetic counselling prior to seeking informed consent.

*‘... as genetic testing moves from dedicated clinical genetics services into mainstream medical clinics, physicians need to be aware of the many challenges associated with contemporary testing.’*

One reason for this ‘special’ status is the potential to ‘unlock’ information that has health implications for a wider circle of family members, for which the patient becomes gatekeeper. As a consequence, the genetic counselling and consent process has typically involved pre-emptive discussions on the implications of the test results, the willingness of the patient to share relevant genetic data with family members and, if appropriate, issues relating to the risks to existing and future offspring.

However, as the landscape of genetic testing changes, so do the considerations relevant to counselling and consent. For example, whilst traditional single gene tests for highly penetrant monogenic disorders have typically given binary results (i.e. positive or negative), the shift towards high-content testing (e.g. disease-targeted gene panels, whole genome sequencing (WGS)) raises many additional issues, not least a substantially increased likelihood of identifying uncertain test results (e.g. variants of uncertain significance, see below) or clinically relevant findings incidental to the indication for testing (i.e. ‘incidental findings’).

*‘Looking forward, it remains unclear how the consent process will evolve, although this is likely to be shaped by a combination of ethical concerns and practical considerations.’*

Indeed, the potential complexities of current high-content testing strategies ensure that it is not feasible to discuss all hypothetical outcomes of testing, although the possibility of ambiguous test results and/or IFs should be discussed, and specific consent sought to determine if ‘actionable’ IFs are to be disclosed.

Furthermore, high-content testing raises additional ethical considerations, including those relating to long term data storage, data sharing (whilst preserving patient privacy) and how to deal with newly available information that may impact upon earlier test results (e.g. variant re-classification, or emergence of new testing strategies).

It seems likely that, in the longer term, out of necessity, we will become more pragmatic about genetic data, and its ‘special’ status will diminish. In addition, the continued exponential rise in genetic testing ensures that existing models of care, based on one-to-one genetic counselling, are increasingly impractical.

Looking forward, it remains unclear how the consent process will evolve, although this is likely to be shaped by a combination of ethical concerns and practical considerations.

## VARIANT INTERPRETATION: DEALING WITH UNCERTAINTY

The clinical utility of a given genetic test is dependent on the accuracy with which the result predicts a health outcome in the individual. For monogenic disorders this is dependent on several factors, including the disease penetrance (i.e. the likelihood that a mutation carrier will manifest disease), clinical expressivity (i.e. the range of phenotypes associated with the genetic abnormality) and, perhaps most importantly, the accuracy of variant interpretation. Unfortunately, many of our prior assumptions regarding these factors have turned out to be inaccurate. For example, both reporting and ascertainment biases have led often to estimates of

*'The recent rapid progress in DNA sequencing technology has far outpaced our ability to accurately interpret the huge wealth of data generated. However, it seems unlikely that we will be able to resist the temptation to deploy testing on a population scale.'*

disease penetrance being substantially overstated, whilst recent large scale sequencing projects have resulted in many previously reported pathogenic variants being reclassified as benign.<sup>3,4</sup>

The majority of molecular genetic laboratories now adopt the American College of Medical Genetics and Genomics (ACMG) guidelines for variant interpretation, which consider multiple variant- and gene-specific features, to categorise variants into one of five groups ('pathogenic', 'likely pathogenic', 'variant of uncertain significance' (VUS), 'likely benign', and 'benign').<sup>3</sup> However, variant interpretation remains imprecise and these groups are not absolute. The VUS designation occurs when there is insufficient evidence to support a more definitive interpretation (either benign or pathogenic), often arising when relevant information is either absent, incomplete or conflicting. With high-content tests, this situation arises frequently, reflected by the observation that ~40% of all variants in the ClinVar database have a VUS designation.<sup>6</sup>

Unfortunately, the 'uncertainty' of a VUS result can spread to the clinician's decision-making. Whilst, by definition, the VUS category is not sufficient to make a molecular diagnosis, it is important to consider the result in the overall clinical context of the patient. For example, how does the result 'fit' with the clinical phenotype and family history? This may help to establish if further clinical follow up or investigation is warranted. In addition, acknowledging that the VUS category covers a range of probabilities, maintaining good lines of communication with the clinical and molecular genetics team may allow a more refined estimate of disease risk. When a VUS is identified, cascade testing of asymptomatic family members is not usually appropriate, although the testing of affected members may increase (or refute) support for pathogenicity.

Finally, it is important to highlight that variant interpretation should not be considered as a static one-off event, but rather as a dynamic process that may change as new information comes to light. As such, establishing procedures that allow periodic re-evaluation of variants is likely to be of benefit.

### STEAMING FORWARD OR 'ICEBERG AHEAD'?

The recent rapid progress in DNA sequencing technology has far outpaced our ability to accurately interpret the huge wealth of data generated. However, as the costs of high-content genetic tests plummet to those of other routinely used diagnostic tools (e.g. cross-sectional imaging), it seems unlikely that, as a profession, we will be able to resist the temptation to deploy testing on a population scale.

For example, many already advocate population-level primary screening for the first wave of hereditary cancer predisposition genes (e.g. *BRCA1*, *BRCA2*, *MLH1*, *MSH2*),<sup>7</sup> whilst arguments extending such testing to additional genes, including those associated with monogenic endocrine tumour disorders (i.e. *SDHB*, *SDHD*, *MEN1*, *VHL*, *RET*) are not likely to be far behind.

However, several studies have reported an unexpectedly high frequency of apparent mutation carriers in the background population, indicating that the implementation of such population-level testing would probably result in a huge demand for downstream tumour surveillance programmes.<sup>3</sup> Therefore, until we have more robust methods for variant interpretation and establishing accurate estimates of disease penetrance, such population-level approaches are likely to prove problematic.

Outside the confines of the medical clinic, the recent US Food and Drug Administration (FDA) approval of the first direct-to-consumer genetic testing for a limited number of *BRCA1/BRCA2* mutations suggests a public appetite for primary prevention genetic testing,<sup>8</sup> and, increasingly, patients are likely to attend medical clinics with the results of genetics tests from private providers. Doctors will need the skills to understand these test results and to determine appropriate courses of action.

*'... until our understanding of the complexity of genetic information and its relevance to health improves, the utility of genetic testing on a global level may be modest.'*

Finally, despite the enormous apparent progress, it remains unclear to what extent the genetic testing revolution will deliver truly transformative health benefits. As we approach the 20-year anniversary of the completion of the first draft of the Human Genome Project, it is worth reflecting how far (or not) we have come. Announcing this event in June 2000, US President Bill Clinton stated: 'Genome science will have a real impact on all our lives – and even more, on the lives of our children. It will revolutionise the diagnosis, prevention and treatment of most, if not all, human diseases.'<sup>9</sup> Nearly two decades later, we remain a long way from such aspirations and, until our understanding of the complexity of genetic information and its relevance to health improves, the utility of genetic testing on a global level may be modest. In reality, the field of clinical genetic testing remains at the start of its journey. As a profession, we probably have no choice but to climb on board, albeit ensuring we have a life jacket packed.

### PAUL J NEWEY

Senior Lecturer and Honorary Consultant in Endocrinology, Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee

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# LOADING THE DICE: GENETIC FACTORS INFLUENCE BMI AND OBESITY

WRITTEN BY SADAF FAROOQI



On the face of it, the rising tide of obesity seems to have little to do with genetics. As a society, we eat more and move less than we need to. Weight gain and, in time, obesity (body mass index (BMI) >30kg/m<sup>2</sup>) follow. However, in an environment where highly palatable, calorie-dense food is cheap and easily available, many people maintain a normal body weight, and some are particularly thin. Why are people so different?

A commonly held view is that people who are obese *choose* to eat more and to exercise less. Obesity is seen as a direct consequence of a lack of willpower and self control: 'It's their fault!' While some people do eat more and move less than others, genetic factors strongly influence these behaviours, and when faced with more calories than we need, genetic factors also influence the amount of weight we gain.

## HOW STRONG IS THE EVIDENCE?

Studies of families, of identical and non-identical twins and of children who were adopted, all indicate that 40–70% of the variation in weight between people is heritable. In a landmark (indeed, heroic) Canadian study, 12 pairs of identical male twins lived under constant supervision for 100 days. They were given a diet that exceeded their energy requirements by 1000 calories a day. Not surprisingly, they all gained weight.<sup>1</sup> The amount gained varied considerably across the group but was very similar between members of a twin pair. Similarly, twins given a reduced calorie diet lost very similar amounts of weight, but across the group there was a lot of variation.

*'There are likely to be hundreds, perhaps thousands, of genes that affect a person's weight.'*

Inherited factors influence how much food we eat, levels of fullness/satiety in response to a fixed meal, basal metabolic rate and the physiological response to a fixed amount of exercise. Lee Kaplan and colleagues showed that the response to bariatric surgery (Roux-en-Y bypass) is highly heritable.<sup>2</sup>

## PUTTING A NUMBER ON IT

One way of assessing the contribution of many different genetic variants to a person's BMI is to add up their effects to derive a risk score. BMI risk scores derived from hundreds of common variants found in genome-wide association studies are higher in obese people than in normal weight people, and very low in extremely thin people.<sup>3</sup>

Recently, Katherisan and colleagues tapped into genetic data from 0.5 million people involved in UK Biobank. By adding up the contribution of 2 million variants they derived a risk score that, for the first time, predicts obesity from age 12 years onwards.<sup>4</sup> Their work, alongside that of others, now unequivocally shows that the dice are loaded against people who develop obesity, and in favour of others who carry variants that protect them from developing obesity<sup>5</sup> and allow a subset of people to stay very thin.<sup>3</sup>

## DOES THIS HELP PATIENTS?

Some healthcare professionals (and indeed politicians) worry that knowing obesity is so strongly influenced by genes will give people permission to eat

what they like 'because it's all genetic'. In practice, this seldom happens. Thinking about other clinical areas, if we recognise the real difficulties that people have with their weight, and why, then we may be able to have a more constructive relationship with patients with severe obesity, which can only be a good thing when managing chronic conditions.

Genetic testing (now available in the NHS) is particularly important in people who develop severe obesity at a young age (before the age of 5 years), who have a high chance of carrying penetrant variants which disrupt the hormone leptin and the hypothalamic neuropeptides and receptors involved in leptin signalling. One condition, albeit rare, responds dramatically to therapy, and there are other genetic obesity syndromes for which targeted clinical trials are ongoing ([www.goos.org.uk](http://www.goos.org.uk)). Importantly, a genetic diagnosis challenges those who advocate removing children with severe obesity from the care of their own families.

## CAN GENETICS REVEAL NEW DRUG TARGETS?

There are likely to be hundreds, perhaps thousands, of genes that affect a person's weight. Finding these genes remains a powerful tool for discovering the mechanisms that regulate weight, which can, in turn, highlight new approaches to therapy.

One example of a potential target informed by genetic studies is *MCR4* (melanocortin 4 receptor), a G protein-coupled receptor which acts in the brain to suppress appetite. People who have variants that disrupt *MCR4* gain weight easily. Different variants in *MCR4* that increase its activity by signalling through the  $\beta$ -arrestin pathway are associated with protection from obesity and its metabolic complications.<sup>5</sup> These studies suggest that drugs that mimic the protective variants could provide new, safer, weight-loss therapies.

So, finally, the evidence is piling up. When it comes to developing obesity, it is now very clear: the odds are stacked against some people and in favour of others.

## SADAF FAROOQI

Wellcome Principal Research Fellow, Professor of Metabolism and Medicine, Wellcome-MRC Institute of Metabolic Science, University of Cambridge, and Honorary Consultant, Cambridge University Hospitals NHS Foundation Trust

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# GENETIC TESTING IN DIABETES

WRITTEN BY SHIVANI MISRA



The recognition of a monogenic form of diabetes dates back to the 1970s, when Robert Tattersall first described maturity-onset diabetes of the young (MODY).<sup>1</sup> As knowledge of the condition has expanded, the initial criteria outlined (autosomal dominant inheritance, age of diagnosis <25 years and no insulin requirement) have been found to recognise some, but not all cases of MODY.<sup>2</sup>

Today, the term monogenic diabetes incorporates not just MODY but other single gene defects causing diabetes, including neonatal diabetes (diabetes presenting at age <6 months) and mitochondrial diabetes (maternally inherited mutations in mitochondrial DNA).

The prevalence of monogenic diabetes varies according to the population studied and how they were selected for testing. MODY accounts for between roughly 1 and 4% of diabetes in those diagnosed below 30 years,<sup>2,3</sup> whilst neonatal diabetes is less common and affects approximately 1 in 100,000 births.<sup>4</sup>

## BENEFITS OF DIAGNOSIS

The impetus to identify monogenic diabetes comes from variable treatment options that depend on the affected gene. In many cases, these options are superior to the standard care provided to people with type 1 or type 2 diabetes, so there is individual clinical benefit in identifying cases.

Mutations in hepatocyte nuclear factor-1 $\alpha$  (*HNF1A*) and -4 $\alpha$  (*HNF4A*),  $\beta$ -cell transcription factors, are best managed with low doses of sulphonylureas.<sup>5,6</sup> Glucokinase (GCK) MODY, involving a key enzyme in glycolysis, requires no treatment at all<sup>7,8</sup> and mutations in hepatocyte nuclear factor-1 $\beta$  (*HNF1B*) are usually insulin-requiring.<sup>9</sup> In neonatal diabetes, the most commonly affected genes are *KCNJ11* and *ABCC8*, encoding the two subunits of the ATP-sensitive potassium channel of the  $\beta$ -cell.<sup>4</sup> High dose sulphonylurea therapy can be used in >90% of cases, without the need for insulin therapy and associated complications in affected neonates.<sup>10</sup>

In addition to being more precise about treatment,<sup>5,11,12</sup> making a diagnosis of monogenic diabetes has other benefits, including cascade testing in family members to identify other cases, and early identification of other features that may be associated with the genetic defect, for example renal abnormalities in people with *HNF1B* MODY.<sup>9</sup> Additionally, delays in diagnosis can impact treatment success. People with *HNF1A* mutations achieved better glycaemic control the earlier a genetic diagnosis was made,<sup>13</sup> and in children with permanent neonatal diabetes, failure to transfer to sulphonylurea treatment completely was associated with a longer duration at the time of transfer from insulin.<sup>10</sup>

## WHAT ARE THE CURRENT CHALLENGES?

### 1. Considering the possibility of diagnosis

A significant proportion of MODY cases remain misdiagnosed as type 1 or type 2 diabetes, whilst new cases are not always recognised, even at diagnosis.<sup>14</sup> The marked geographical variation in frequency of genetic test requests signals variation in clinical practice, but this heterogeneity is likely to improve following efforts from the Exeter Molecular Genetics team to improve education, and a network of genetic diabetes nurses to facilitate training and testing.<sup>15</sup>

### 2. Deciding to test

A stratification process is required to identify the cases most likely to have monogenic diabetes. For neonatal diabetes, this is relatively straightforward, as the phenotype of developing diabetes in the first 6 months of life is unambiguous, nearly always monogenic, and testing is available free of charge.<sup>4</sup> For cases of MODY, clinical stratification (selecting those diagnosed below 30 years) with biomarkers (selecting only those negative to pancreatic autoantibodies, with some evidence of endogenous C-peptide production) seems to be the most effective approach.<sup>2</sup>

### 3. Diagnosis in ethnic groups

Whilst initial studies to identify monogenic diabetes have focused on white European populations, there is now increasing recognition of monogenic diabetes in people of other ethnicities.<sup>16</sup> However, a 2016 study revealed that the detection rate for MODY in South Asian people referred for genetic testing was much lower than in people of white ethnicity.<sup>17</sup> It is likely that more people will need to be tested from ethnic groups with a high prevalence of young-onset type 2 diabetes, as the separation of MODY from type 2 diabetes is challenging on the basis of clinical features and existing biomarkers.<sup>18</sup>

### 4. Understanding test results

Anyone undertaking genetic testing in their practice will have come across novel mutations or variants of unknown significance (VUS) in genetic testing reports.<sup>19</sup> Understanding what these results mean, whether they should be conveyed to the patient and how they might impact treatment is challenging. Co-segregation studies in family members can be a powerful tool, along with detailed clinical phenotyping, to disentangle pathogenicity.<sup>20</sup> Sometimes clarity around diagnosis cannot be provided, and it is good clinical practice to keep a record of patients with these variants which can be revisited regularly with the molecular genetics service, as more knowledge becomes available.

## NEW DEVELOPMENTS IN THE FIELD

To date, the field of diabetes genetics has focused on detecting monogenic disorders, but now attention is turning to utilisation of information about the polygenic risk of diabetes. Single nucleotide polymorphisms (SNP) can modify the risk of type 1 and type 2 diabetes, both polygenic conditions. Summing up the risk of individual SNP genotypes can provide a composite polygenic risk score. In diabetes, these risk scores have been used to support diabetes classification, given the challenge of differentiating type 2 diabetes from adult-onset type 1 diabetes and also MODY.<sup>21,22</sup> The impact of using this clinical information and its applicability in all ethnicities have yet to be determined, and those in the field await further studies.<sup>23</sup>

## SHIVANI MISRA

Consultant in Diabetes and Metabolic Medicine, Imperial College Healthcare NHS Trust, London

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# MOLECULAR MARKERS IN DIAGNOSING THYROID CANCER

WRITTEN BY KRISTIEN BOELAERT



The majority of thyroid cancers are differentiated, originating from follicular thyroid cells. They usually present as a lump in the neck or may be found incidentally during investigation of unrelated neck disorders, including carotid Doppler and cross-sectional imaging approaches.

Thyroid nodules (lumps) are very common and occur in at least 50% of the population. However, only a small subgroup (5–7%) harbour a clinically significant cancer. The initial evaluation of thyroid nodules includes thyroid function testing, to ensure this is normal, and an ultrasound assessment. There are a number of scoring systems which combine suspicious ultrasonographic features such as solid composition, hypoechogenicity, irregular margins, increased intra-nodular blood flow and the presence of micro-calcifications to predict the risk of malignancy.

Nodules that cannot be deemed benign through ultrasonography need to be further investigated through fine needle aspiration cytology (FNAC), to help determine the possible presence of thyroid malignancy.<sup>1</sup>

## INDETERMINATE THYROID NODULES

Around 20–30% of cytological evaluations result in indeterminate results and usually encompass RCPATH Thy3a (neoplasm possible with cellular atypia) and Thy3f (follicular neoplasm suspected), which have an overall risk of malignancy of 10–30% and 25–40% respectively.

Generally, patients with indeterminate nodules undergo surgery to remove the half of the thyroid gland that contains the thyroid nodule for full pathological evaluation, to exclude thyroid malignancy. The use of molecular testing of FNAC specimens to refine the diagnosis of thyroid malignancy has become widely accepted in the USA and in some European centres.<sup>2</sup>

## GENETIC ALTERATIONS

The molecular alterations underlying thyroid cancer have been unravelled for about 95% of differentiated tumours. Papillary thyroid cancers, which account for about 85% of all thyroid cancers, usually occur following mutations in genes coding for proteins in the mitogen-activated protein kinase (MAPK) pathway, which regulates the proliferation and differentiation of thyroid cells. A single mutation in the *BRAF* gene (V600E) is found in up to 60% of papillary cancers, as well as in more rare poorly differentiated and anaplastic cancers, which originate from papillary cancers following a de-differentiation process. Mutations in *RAS* genes are found in 15% of papillary cancers and in 40% of follicular cancers, which also belong to the group of differentiated cancers, accounting for 2–5% of all thyroid cancers.<sup>3</sup>

Hybrid genes, formed following fusion of two previously unrelated genes, such as the *RET/PTC* oncogene and the *PAX8/PPARG* gene, are found in radiation-induced papillary cancers and in some follicular thyroid tumours. More recently, mutations in the telomerase reverse transcriptase (*TERT*) gene and in the *TP53* tumour suppressor gene have been described in some differentiated tumours, but also, in particular, in undifferentiated and anaplastic thyroid tumours.<sup>3</sup>

## MOLECULAR TESTING STRATEGIES

The two most commonly used approaches to evaluate the molecular background of thyroid cancers are mutational analysis and gene expression analysis.

In mutational analysis, the DNA from the material obtained through fine needle aspiration biopsy of the thyroid nodule is sequenced to look for mutations in *BRAF*, *RAS*, *TERT*, *TP53* and other relevant genes, as well as to detect fusion genes.<sup>4</sup> If a mutation in these genes is found, then thyroid

cancer is almost always present, and this type of testing is therefore called a 'rule-in' test.<sup>5</sup>

However, *RAS* mutations may be present in benign thyroid lesions and driver mutations are unknown for about 5% of differentiated cancers, so false-positive and false-negative results may occur. Nonetheless, this approach offers further advantages because the determination of *BRAF*- and *RAS*-positive status also has prognostic value in addition to diagnosing thyroid malignancy. *BRAF*-positive tumours are more aggressive whereas *RAS*-positive cancers tend to have a more indolent behaviour.<sup>6</sup>

Gene expression analysis or gene expression classifiers use algorithm-type approaches to analyse the expression of specific genes in panels of 142 genes.<sup>7</sup> Nodules are classed as benign or suspicious, with those identified as benign not requiring surgery. This is therefore a 'rule-out' test, and a pooled analysis of 12 studies concluded that the negative predictive value of the gene expression classifier is 92%, with a malignancy prevalence rate of 31%, in the nodules that were studied.<sup>8</sup>

A further approach to diagnose the presence of malignancy is the determination of expression of microRNAs, which are small non-coding RNA fragments that regulate gene expression by influencing the stability and translation of messenger RNA. MicroRNAs are relatively stable compared with messenger RNA and are differentially expressed in benign and cancerous thyroid tissues. Two commercially available kits based on microRNA expression in thyroid fine needle aspiration biopsies are currently in use.<sup>9</sup>

## MOLECULAR TESTING IN THE NHS

Molecular testing to avoid unnecessary surgery in patients with indeterminate thyroid nodules is expensive, ranging from \$3000 to \$5000 depending on the test used. The most studied tool evaluated on health economic grounds is the gene expression classifier, indicating this to be a cost-effective test.<sup>10</sup> However, most of these cost-effectiveness analyses are based on modelling rather than actual patient data, and results are dependent on the malignancy rates in the population, costs of surgery and surgical complications, healthcare costs and a number of other factors.

Whilst these molecular analyses are likely to result in reductions in unnecessary surgery and patient benefit, the high cost of testing makes the routine use of these approaches prohibitive in our current NHS system.

## KRISTIEN BOELAERT

Reader in Endocrinology, Institute of Metabolism and Systems Research, University of Birmingham

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# GENE THERAPY: A NEW HORIZON

WRITTEN BY YALDA JAMSHIDI



In 1989, the discovery of the gene that is defective in the childhood disease cystic fibrosis brought about the hope of treating this, and similarly devastating genetic diseases, by targeting the defective gene itself. We call this approach gene therapy.

Diseases such as cystic fibrosis are known as ‘rare’ diseases, but whilst individually a rare disease can affect just a handful of people, collectively the numbers are much more alarming. For instance, in the UK alone, up to 3.5 million people will be affected by a rare disease at some point in their lives.

Up to 80% of these rare diseases are genetic in origin and, with recent advances in genetic sequencing technologies, the rate of successful diagnoses has increased dramatically. Unfortunately, for the overwhelming majority of these patients, there is still no treatment.

Since that first disease-gene discovery 30 years ago, researchers have been testing different approaches to gene therapy. These have included limiting or switching off expression of the gene, replacing it with a healthy copy, or increasing the activity of an alternative gene that can compensate for the deficient one. Success relies on being able to carry out targeted alterations of DNA sequences, but also on the ability to get the gene to the right organ – the problem of gene delivery.

For many years gene therapy trials had limited success, resulting in adverse reactions, most notably the case of Jesse Gelsinger, an 18-year-old with a rare liver disorder, who died from multiorgan failure following gene therapy in 1999.

Any new treatment or drug comes with a risk of adverse events. However, in the case of an individual rare disease, standard trial designs often cannot be easily optimised to obtain adequate safety and efficacy data, due to the small numbers of patients available. As a result, alternative designs have had to be developed. Thanks to legislative incentives for developing orphan drugs to target rare diseases, there has been substantial progress over the past 20 years.

Excitingly, a string of recent success stories has returned some hope to the field. These have included the first US Food and Drug Administration (FDA)-approved gene therapies for an inherited eye condition (*RPE65*-mediated retinal dystrophy), and a severe neuromuscular condition (spinal muscular atrophy; SMA), and phase 3 gene therapy trials for a severe skin-blistering condition (epidermolysis bullosa).

Another important recent development has been the advent of a new powerful technique for gene editing, known as CRISPR. This technique allows researchers to edit DNA much more cheaply, accurately and simply than ever before. It has quickly led to a series of clinical trials to test safety and efficacy of CRISPR-mediated gene therapies for debilitating genetic diseases.

CRISPR relies on the use of proteins used by bacterial cells to fight viruses. For effective gene delivery it is often coupled with the use of adeno-associated viruses (AAVs). These viruses have been modified to function as delivery agents. They have been used over the years in gene therapy trials, including, for example, the recent successful SMA trial.

However, since CRISPR technology is relatively easy to implement, it can also be abused. Last year, news of an unregulated, unethical use of CRISPR technology to edit the DNA of otherwise healthy human embryos threatened to slow down the excitement and progress of CRISPR-based gene therapies. Altering genes in human embryos means that offspring will

inherit the changes, potentially leading to unpredictable effects on future generations. In reaction to the news, some of the scientific community released a statement asking for a global moratorium on all clinical uses of human germline editing.<sup>1</sup>

Yet, the technology is immensely valuable in disease research and for the treatment of many serious inherited conditions, a distinction highlighted in the statement. Unlike the controversial germline gene editing, CRISPR-based human clinical trials have thus far been limited to somatic cells. In other words, as with any experimental drug or treatment, they have no consequence for future generations.

*‘Whilst individually a rare disease can affect just a handful of people, collectively the numbers are much more alarming ... in the UK alone, up to 3.5 million people will be affected by a rare disease at some point in their lives.’*

For example, earlier this year, CRISPR Therapeutics and Vertex Pharmaceuticals announced the first dosing of a patient with a severe haemoglobinopathy using a gene-edited cell therapy, called CTX001, in a phase I/II trial.<sup>2</sup> This trial involves gene editing the cells outside the body, then reintroducing them into the patient.

The first *in vivo* (i.e. editing inside the body) CRISPR-based therapeutic, EDIT-101, is also being investigated. Editas Medicine Inc. published their preclinical data on EDIT-101, which will be administered to patients with a genetic form of blindness.<sup>3</sup>

As with any new therapeutic development, there will be elements of uncertainty. However, for families living each day with the real burden of genetic disease, this uncertainty will need to be balanced against the potential benefits and, ultimately, patient choice.

Following decades of development, there lies ahead an exciting path towards finally realising those initial hopes of gene therapy as a promising treatment option for families affected by a rare disease.

**YALDA JAMSHIDI**

Reader in Genomic Medicine and Head of Genetics Research Centre, Molecular and Clinical Sciences Institute, St George’s University of London

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# Celebrating and rewarding **EXCELLENCE IN ENDOCRINOLOGY**

Join us in congratulating our 2019 Society medal winners, world leaders in endocrinology, whose work continues to advance our knowledge and clinical practice in endocrinology. Our medallists will present plenary lectures at the Society for Endocrinology BES conference 2019 on 11-13 November in Brighton.

## MEDAL LECTURERS



**DALE  
MEDALLIST**  
Constantine Stratakis  
Bethesda, MD, USA



**SOCIETY  
MEDALLIST**  
Philippa Saunders  
Edinburgh, UK



**STARLING  
MEDALLIST**  
Markus Ralser  
London, UK



**TRANSATLANTIC  
MEDALLIST**  
Michael Whyte  
St Louis, MO, USA



**EUROPEAN  
MEDALLIST**  
Felix Beuschlein  
Zurich, Switzerland



**INTERNATIONAL  
MEDALLIST**  
Roger Cone  
Ann Arbor, MI, USA



**JUBILEE  
MEDALLIST**  
Julian Davis  
Manchester, UK

### HELP CHOOSE OUR 2020 MEDAL WINNERS

*Who do you think deserves to be recognised for their contributions to endocrinology next year?*

For more details and to nominate, visit [www.endocrinology.org/grants-and-awards/prizes-and-awards/medals](http://www.endocrinology.org/grants-and-awards/prizes-and-awards/medals).

Nominations must be received by **8 July 2019**.

### APPLICATIONS OPEN FOR ENDOCRINE NURSE AWARD

*Are you a nurse leading an innovative initiative in endocrinology?*

*Do you know an endocrine nurse that deserves recognition for their contributions to patient care, education or research?*

Apply, or nominate a colleague, for the 2020 Endocrine Nurse Award by **8 July 2019**.

For more details visit [www.endocrinology.org/grants-and-awards/prizes-and-awards/endocrine-nurse-award](http://www.endocrinology.org/grants-and-awards/prizes-and-awards/endocrine-nurse-award).

## Inspiring future endocrinologists WITH A TASTE OF SFE BES

What would it have been like for you to experience your first Society for Endocrinology BES conference even before you finished school, when you were still embarking on your first steps towards a scientific or medical career?

Well that's exactly what the Society has been able to offer around 50 lucky school pupils each year, starting at the Society for Endocrinology BES conference 2017 in Harrogate. The aim is to bring endocrinology to life and to demonstrate its value in the everyday world and in careers.

The Society for Endocrinology BES conference 2018 in Glasgow was no different, and we welcomed pupils from local Glaswegian schools to the Scottish Event Campus to come and meet the scientists, nurses and clinicians who make up the Society's membership.

For one afternoon during the conference, pupils were able to attend their own dedicated conference session, which started with an overview of hormones given by Maralyn Druce. Pupils then rotated around four hands-on activities that provided them with a taste of some of the many flavours of hormone science, from 'pin the hormone' (Rosemary Bland & Matt Simmonds) and 'cell signalling' (Nigel Page) to 'circadian rhythms' (Francesca Spiga) and 'blood glucose' (Channa Jayasena & Lisa Shepherd).

Scan to find out  
more about insulin

[www.yourhormones.info](http://www.yourhormones.info)



Society for  
Endocrinology

The cell signalling even included its own light and sound display, while Matt Grant had devised a series of Society for Endocrinology-branded QR-coded cards, which students

could take home in order to learn more about hormones at their leisure, by linking to the Society's You and Your Hormones website ([www.yourhormones.info](http://www.yourhormones.info)).

Two networking sessions followed, one each for scientific and clinical careers, with plenty of time for pupils to ask all their questions in an informal setting.



The schools' conference session provided a great way for members to get involved in showcasing some of the Society's public engagement activities. We are grateful to the 22 members who volunteered at this year's event.

And what did the pupils and their teachers have to say?

*It gave me a first-hand perspective on how individual various careers are.*

*I learned from real-life scientists about the things/experiences I need for my future.*

*It made me certain that my choice of career was for me.*

*The practical aspect was engaging and enjoyable.*

Pupils, Schools' Conference Session, 2018

*Thank you for a lovely afternoon, it was very informative.*

*All the scientists and medics were lovely and very approachable, and the pupils have gained a lot from this.*

Teachers, Schools' Conference Session, 2018

### YOU TOO CAN BE INVOLVED!

We are already planning for the Society for Endocrinology BES conference 2019 in Brighton in November. Perhaps you are considering your first steps into public engagement and want to learn a bit more? Maybe you have a fantastic activity you'd like to showcase?



Alternatively, if you've got an idea that you would like to develop and demonstrate, you could apply for one of the Society's Public Engagement Grants (see page 3, deadline 25 September 2019). Whichever way, please do get in touch.

It is very rewarding and enjoyable to get involved in public engagement and outreach with the Society! For further informal discussion about getting involved, please contact [media@endocrinology.org](mailto:media@endocrinology.org).

#### NIGEL PAGE

Public Engagement Committee member and Endocrine Ambassador at Kingston University London

# Get excited **ABOUT BRIGHTON**

Join us on the **11-13 NOVEMBER 2019**  
for this year's Sfe BES conference!

Come to Brighton and connect with hundreds of friends, colleagues and newcomers to the UK's biggest endocrine community. Exchange knowledge and experiences, create new opportunities to collaborate and strengthen your outcomes in endocrinology at **Sfe BES 2019**.



**A NEW, MODERN PROGRAMME** minimises the chances of frustrating clashes by reducing the parallel streams from four to three whilst ensuring both oral communications and symposia are run in tandem.

We're also extending lunch to 90 minutes, giving you the time you need to network with friends and colleagues, visit the exhibition hall and comfortably attend industry symposia.

These improvements combine to provide you with the best Sfe BES experience to date.

## **EMPOWERING THE ENDOCRINE NETWORKS**

The Society's Endocrine Networks have created a community of Society members working in a particular subspecialty of the field. Connect with peers and international leaders in your area of expertise for a focused symposium on Wednesday 13. Attendees will meet colleagues experiencing the same challenges and looking for opportunities to collaborate.

**The Endocrine Network sessions are:**

- Adrenal and Cardiovascular
- Bone and Calcium
- Endocrine Consequences of Living with and Beyond Cancer
- Endocrine Neoplasia Syndromes
- Metabolic and Obesity
- Neuroendocrinology
- Reproductive Endocrinology and Biology
- Thyroid

**THE Sfe THEATRE** is the brand new presentation area at the heart of this year's exhibition hall. This new space provides you with numerous opportunities for learning, with 'lightning talks' and bespoke product demonstrations relevant to your specialism.

**INNOVATION SESSIONS** will cover clinical, basic science and industry innovation crucial to your work. Attend and expose yourself to novel technologies, developments in clinical practice and new opportunities for funding. You'll also gain awareness of opportunities for collaboration that have yet to be discussed anywhere else.

**TUESDAY IS FOR NURSES** thanks to a streamlined programme, built with nurses in mind. This year's nurse events avoid clashes with the equally popular 'How do I' sessions, ensuring you can attend all activities aimed at improving your clinical outcomes. It's also easier than ever to meet and network with fellow nurses at our social evening on Monday and dedicated lunch session on Tuesday.

Find out what's new at  
[www.endocrinology.org/sfebes2019](http://www.endocrinology.org/sfebes2019)



11-13 November  
BRIGHTON



**ABSTRACT  
SUBMISSION DEADLINE**  
1 July 2019 (23.59 BST)

**EARLY BIRD  
REGISTRATION  
DEADLINE**  
5 September 2019  
(23.59 BST)

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Save  
the date



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# Expand your professional community CONNECT WITH YOUR ENDOCRINE NETWORKS

The Society's Endocrine Networks are designed to enable basic and clinical researchers, clinical endocrinologists and endocrine nurses to share knowledge and best practice, and to work together to advance their specialist fields. Find out more at [www.endocrinology.org/membership/endocrine-networks](http://www.endocrinology.org/membership/endocrine-networks).



## MEET YOUR ENDOCRINE NETWORK CONVENORS

### ADRENAL AND CARDIOVASCULAR

**Scott MacKenzie** Glasgow



### METABOLIC AND OBESITY

**Barbara McGowan** London  
**Kevin Murphy** London



### BONE AND CALCIUM

**Jeremy Turner** Norwich  
**Caroline Gorvin** Birmingham



### NEUROENDOCRINOLOGY

**Niki Karavitaki** Birmingham  
**Craig Beall** Exeter



### NEW! ENDOCRINE CONSEQUENCES OF LIVING WITH AND BEYOND CANCER

**Helen Simpson** London  
**Claire Higham** Manchester



### REPRODUCTIVE ENDOCRINOLOGY AND BIOLOGY

**Andrew Childs** London  
**Kim Jonas** London



### ENDOCRINE NEOPLASIA SYNDROMES

**Paul Newey** Dundee



### THYROID

**Carla Moran** Cambridge



## INTRODUCING OUR NEW ENDOCRINE NETWORK ENDOCRINE CONSEQUENCES OF LIVING WITH AND BEYOND CANCER

Endocrine Network convenors Helen Simpson and Claire Higham look forward to hearing from anyone with an interest in research and clinical care associated with endocrine-related effects of cancer. You can contact them on SfE Connect.

#### Key topics of the Network:

- Endocrine and metabolic consequences of cancer and cancer therapies
- Electrolyte disturbances such as hyponatraemia and hypo- and hypercalcaemia
- Immunotherapy toxicities
- Endocrine consequences of proton beam therapy
- Bone health
- Progress towards recommending interventions and surveillance strategies

## JOINING OUR ENDOCRINE NETWORKS IS EASY:

Log into the Members' Area at [www.endocrinology.org/members](http://www.endocrinology.org/members)

Select 'Endocrine Networks'

Tick the all the Networks you'd like to join!

## JOIN SFE CONNECT TODAY!

Keeping informed and up-to-date with your Endocrine Networks is now even easier. Using the Society's new online community tool, SFE Connect, you can start new conversations to help grow your Network by sharing knowledge and best practice and working together to find solutions to challenges within your field.

To join, simply visit <http://sfconnect.onsocialengine.com/>, select 'Request invite' and enter your name and email address.

**SFE CONNECT** can help you:

- Inform other members about what's new in your field
- Get advice or expertise from Network members
- Catalyse new collaborations within the Network and beyond

- Promote new posts or meetings of interest to Network members
- Arrange offline meetings with members for more in-depth discussions
- Discuss any issues relevant to your work and the wider endocrine community
- Share knowledge and best practice

Join **SFE CONNECT** to access exclusive Society for Endocrinology BES conference 2019 news and views, especially for SFE Connect members!



## HELP SHAPE YOUR ENDOCRINE NETWORK

Want to get more involved with your Network?

You can apply to be a convenor. Each Network has a clinical and a basic scientist focused convenor, for a term of 4 years. Society members can apply themselves or nominate others.

Visit [www.endocrinology.org/membership/endocrine-networks](http://www.endocrinology.org/membership/endocrine-networks) to download a nomination form.



## WHAT COULD YOU DO WITH AN ENDOCRINE NETWORK GRANT?

Grants of up to £5000 are available to support any Network activities, including:

- organising an event
- funding collaborative research initiatives
- employing staff to administer clinical data collection
- supporting any relevant Network activity you can think of!

To find out how to apply, contact [grants@endocrinology.org](mailto:grants@endocrinology.org) with your proposal.

## ANNE MARLAND

NURSE COMMITTEE CHAIR



The lighter, warmer evenings of summer give us all greater inspiration to read more and reflect upon our careers, and to consider how we are evolving and engaging professionally as endocrine nurses.

Sofia Llahana's article introducing *Advanced Practice in Endocrinology Nursing*, the first textbook aimed at nurses, provides us with a thorough appraisal of this publication (see page 29). It is a testament to what can be achieved through collaborative work, and importantly includes contributions from patients and patient advocacy groups, which support inclusion and transparency in shared decision making in patient care.

The book will support you to advance your practice, underpinned by the Society for Endocrinology Competency Framework for Adult Endocrine Nursing (*Endocrine Connections* 2015 4 W1–W17). It is available in print or as an ebook so, whether you're a techie or a technophobe, you can discover what it has to offer to you and your departments.

Talking of amazing successes, Endocrine Nurse Update in Birmingham was full to capacity. I would like to thank all of you who attended and actively contributed, as the success is a testament to your active participation.

Our next event will be the Society for Endocrinology BES conference in Brighton in November. Please join us for our exciting nurses' programme, which includes two dedicated nurse sessions with eminent speakers (see panel and [www.endocrinology.org/sfebes2019](http://www.endocrinology.org/sfebes2019)). I also encourage you to submit an abstract (guidance provided on this page) by the deadline of 1 July. This will make you eligible for a travel grant to attend ([www.endocrinology.org/grants-and-awards](http://www.endocrinology.org/grants-and-awards)).

I hope you all have a lovely summer.

BEST WISHES

ANNE MARLAND

### NURSE SESSIONS AT SFE BES 2019

#### NICE and T3

- T3 replacement: what does the evidence suggest?
- The healthcare professional and patient consultation – informed decision making
- A beginners' guide: setting up a nurse-led thyroid clinic

#### Management of hyper- and hypocalcaemia

- Aetiology of hyper- and hypocalcaemia
- Patient management of hypercalcaemia and when should the surgeon intervene?
- Patient management of hypocalcaemia and the patient perspective

## SUBMIT AN ABSTRACT TO SFE BES 2019

By submitting your abstract to the Society for Endocrinology BES conference 2019, you'll be exposing your work to over 1000 clinicians, nurses and researchers in endocrinology from across the UK and further afield. Those who submit raise their profile within their specialty, whilst also gaining increased opportunities to collaborate.

There is a specific abstract category for Nursing Practice, and we urge you to consider submitting

Accepted abstracts are presented at the event as a poster, eposter or oral presentation. They will also be published online in *Endocrine Abstracts*. The abstract should be no longer than 300 words (including numbers, symbols and tables). The full format and guidelines for abstracts can be seen in the online submission form.

The deadline for receipt of abstracts is 1 July 2019 (23.59 BST). Submit at [www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2019/abstracts](http://www.endocrinology.org/events/sfe-bes-conference/sfe-bes-2019/abstracts).



# INTRODUCING ADVANCED PRACTICE IN ENDOCRINOLOGY NURSING

WRITTEN BY SOFIA LLAHANA



## Advanced Practice in Endocrinology Nursing

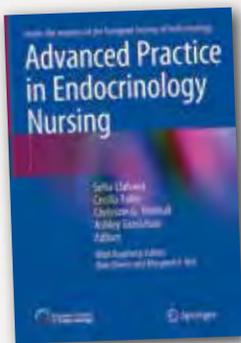
Eds S Llahana, C Follin, C Yedinak & A Grossman

2019, Springer, 1337 pp, colour

Hardback: £92.00, 2 vols  
ISBN 978-3-319-99815-2

eBook: £73.50  
ISBN 978-3-319-99817-6

Section Editors: K Davies & M Keil (for paediatric sections), J van Eck, V Fazal-Sanderson, G Conway, A Dwyer, A Robinson, P Yeoh, A Marland & M Tadman



resource for practitioners in other specialties, such as fertility, osteoporosis, oncology, urology, gynaecology, and obesity and metabolic disorders, as well as specialty trainees, general practitioners, students and expert patients.

We anticipated and, indeed, faced many challenges in undertaking this project, especially as the role of the endocrine nurse, and nursing training and qualifications, vary significantly from country to country. We were, however, overwhelmed by the interest we received from colleagues who wanted to contribute to this book, echoing the great need for such a resource. In particular, this came from physicians and other healthcare professionals who recognise the endocrine nurse as a vital member of the multidisciplinary team.

## CONTRIBUTORS AND STRUCTURE

ESE formed our initial working hub and supported this textbook from its inception. We created a strong collaborative international network: 118 eminent authors from 15 countries contributed to this book. Our authors are nurses, physicians, surgeons, psychologists, dieticians, clinical scientists and geneticists, emphasising the multidisciplinary focus of the book.

Each chapter includes a comprehensive review of the anatomy, pathophysiology, diagnosis and treatment of different endocrine conditions, supported by the latest evidence and clinical guidelines. Patient stories, case studies and examples of good clinical practice are included, to illustrate the impact of endocrine conditions on patients and their families. These also stimulate the readers' critical thinking and reflection, and make information in this book applicable to their practice. Many patient advocacy groups contributed case studies and educational resources, supporting the importance of user involvement and shared decision-making in patient care.

The book comprises 13 sections and has a total of 69 chapters. Our section editors played a vital role in inviting authors and editing the chapters in each section. Each section covers conditions relating to a specific endocrine gland (pituitary, adrenal, thyroid, parathyroid and bone disorders, and male

We are very pleased to introduce the first book ever published for endocrine nurses, which has been produced under the auspices of the European Society of Endocrinology (ESE).

We identified the need for an evidence-based published resource to support endocrine nurses in advancing their practice, underpinned by the competence frameworks developed by our British colleagues.<sup>1,2</sup> Significant but isolated clinical and research expertise was evident amongst our colleagues in the UK and internationally. We therefore formed an international network, in order to develop a comprehensive resource to support endocrine nurses around the globe. These colleagues work at different settings and levels of practice, from novice to expert, and from bedside nursing to advanced practice nursing, running independent nurse-led services.

Recognising the importance of multidisciplinary working, we also wanted this book to be a useful

and female reproduction) and other relevant endocrine conditions, such as late effects of cancer treatment, neuroendocrine tumours, endocrine emergencies, and obesity and metabolic disorders.

There are two sections specific to paediatrics (11 chapters). Paediatric aspects have also been incorporated into many other chapters, where relevant. The final section focuses on advanced practice nursing, presenting an overview of role development and the definition and components of advanced practice nursing, including research.

## IMPLEMENTATION AND FUTURE DEVELOPMENTS

*Advanced Practice in Endocrinology Nursing* is currently the only comprehensive evidence-based clinical reference for endocrine nurses. As such, it can be used alongside the *Competency Framework for Adult Endocrine Nursing*,<sup>2</sup> to support the progression of nurses' careers 'from novice to expert'. In combination, they provide a framework for nurses to identify their personal educational and developmental needs and a 'one stop shop' resource to enhance their knowledge and competence.

The last section of the book is particularly useful, as it provides evidence-based and practical resources to support career progression and role development towards advanced nursing practice.

Division of the book into sections provides in-depth knowledge for nurses who want to develop expertise in specific areas within endocrinology: for example, reproduction or women's health. This presents opportunities for professional development and education, by helping nurses to identify and bridge knowledge gaps. Each chapter also includes key reading and comprehensive reference lists of significant and current evidence on the subject. This can also provide stimuli to generate research questions and collaborative multidisciplinary working to improve patient care.

The book was formally launched at the European Congress of Endocrinology on Sunday 19 May 2019. We held two workshops (on acromegaly and adrenal insufficiency), illustrating the book's role in supporting development of evidence-based knowledge, using the *Competency Framework*. We will continue to develop and deliver further workshops and online webinars, and anticipate this book will be a key reading reference on curricula for advanced nursing practice and endocrine academic courses.

## CONCLUSION

*Advanced Practice in Endocrinology Nursing* is a testament to what can be achieved when everyone works collaboratively towards the shared objective of advancing our profession and improving patient care. We developed a comprehensive evidence-based resource, which we hope and trust will assist and advise all our colleagues, to ensure the best possible patient care and to raise the profile of endocrine nursing around the globe.

## SOFIA LLAHANA

Senior Lecturer and Programme Director, MSc Advanced Clinical Practice, School of Health Sciences, City, University of London; Hon Consultant Nurse in Endocrinology, University College Hospital, London

## REFERENCES

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## SAFFRON WHITEHEAD

Saffron Whitehead, Emeritus Professor of Endocrinology, sadly passed away on 18 February 2019. She had been an active member of the Society for Endocrinology for many years.

A long-serving member of the Editorial Board of *The Endocrinologist*, Saffron was the magazine's Editor from 2004 to 2005. She was the Chair of the Public Engagement Committee, and also managed press enquiries regarding publications and scientific breakthroughs for the Society. Saffron was a dedicated advocate for women's health and worked across the media to increase the public awareness of endocrine issues.

Professor Whitehead graduated from University College London in 1970 with a degree in physiology. Having come relatively late to her degree, she felt that she had finally found her life's purpose. In particular, she became fascinated by endocrinology, moving to McMaster University in Hamilton, Ontario, Canada, to study for her PhD in neuroendocrinology. Her first publication from this work appeared in *Brain Research* in 1974. It was soon after this that she began to study the impact of endocrine-disrupting chemicals, an area of research that remained a life-long interest. Her expertise made her a national spokesperson on the subject for the press and media.

*'Saffron was a dedicated advocate for women's health and worked across the media to increase the public awareness of endocrine issues.'*

Moving back to the UK, she joined St George's Hospital Medical School, London, in 1978, as Lecturer in Endocrinology and Reproduction. She remained active in research there until her retirement in 2013, after which she was granted emeritus status.

Consistently gaining promotion while raising a family, Saffron was an important role model for younger female staff in the medical school, being one of only a small number of female professors at St George's for most of her career. Saffron was a gifted teacher and her endocrinology lectures and the specialist course that she established, entitled 'Science of Reproduction', were always the most popular. Although officially retired, she remained active as a tutor and teacher at St George's until very recently.

Saffron was prolific author and, in fact, her latest book, *Managing Obesity: a Practical Guide for Clinicians*, was published with co-author Gul Bano earlier this year. Across her academic career, she published 55 notable papers, five reviews and three endocrinology textbooks. Her textbooks became definitive texts on many university degree courses, and she won Academic Textbook of the Year for *Endocrinology: an Integrated Approach*, authored with Steve Nussey.

Saffron wrote widely across her career for publications as diverse as *New Scientist* and *The Guardian* and she won a sabbatical award from The Wellcome Trust to focus on her media writing. She also contributed regularly to TV and radio, including appearances on BBC4's 'The Fantastical World of Hormones' and BBC Radio 4's 'Women's Hour'. She was the scientific advisor on 'Tide Tables' a 2011 play supported by the Wellcome Trust and the Society for Endocrinology. The play centred on the challenges of midlife as a time of significant biological change.



*'Consistently gaining promotion while raising a family, Saffron was an important role model for younger female staff in the medical school, being one of only a small number of female professors at St George's for most of her career.'*

Saffron was a thoughtful and supportive colleague and supervisor, who gave willingly of her vast fount of knowledge and wisdom. Following 'retirement' Saffron continued to dedicate her time to others and became a governor for Oak Lodge School for the Deaf. In addition, she volunteered with the Shaw Trust, a charity helping people to rebuild their lives and re-enter work and education. Saffron was a keen tennis player and took an active role in the local tennis club.

The recent additions to the family saw her once more also taking an active role in childcare, albeit this time being able to hand them back at the end of the day!

Saffron's warmth and wit will be missed by colleagues, students and friends alike. She is survived by her husband John Davies, three sons, daughters-in-law and four grandchildren.

**HELEN MASON**  
EduLink Consultants, Dubai, UAE

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This issue's photo was taken by Kenny Muir (Inverness). Kenny says 'The image was taken in Glen Affric, Scotland, in January 2019. I had to take advantage of the full early morning cortisol peak to cope with the  $-12^{\circ}\text{C}$  temperature nadir!'



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PP-RDP-GBR-0127  
Date of preparation - April 2019