How are advances in genomics impacting on pathology and patient care?

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Defined by the Royal College of Pathologists as "the study of the body's genes, their functions and their influence on the growth, development and working of the body"[1], genomics expands upon the definition of "genetics" as we understand it. It looks at the entirety of an individual's genetic code, not just the genes that code for proteins, but non-coding regions - which are now understood to play a significant role in the expression of our genetic code and the interaction between different genes[2]. Therefore one's "genome" is the full genetic code of an individual. Genomics may also investigate pathogens to elucidate information to aid in more precise drug treatment[3].

With the advent of next generation sequencing [NGS] and whole genome sequencing [WGS], reading the full genetic code became a viable procedure in the pathological investigation of diseases. Greater uptake of this technology may potentially revolutionise the way in which clinicians assess risk, diagnose, and prioritise treatment options, thereby potentially improving prognosis for patients[4,5]. Examples include lung and colorectal cancer patients where NGS is being used to direct treatment, but this is not yet the common approach[6,7]. Other instances include the case of a 4-year-old with a glucose metabolism disorder, diagnosed via WGS. This diagnosis directed dietary changes meaning improvement of their symptoms[4]. Another is that of a 10-year-old who had a life-threatening varicella infection. WGS identified a *CTPS1* mutation and diagnosed immunodeficiency. This directed clinical management and referral for a potentially curative haematopoietic stem cell transplant[4].

For the pathologist, the greatest change to their role due to uptake of genomic technology will be seen in the treatment of cancer. Where previously immunohistochemistry indicated the distribution and parent-tissue of a cancer based on antigen expression, there will be widespread genomic assessment of tumours[8]. Genomics details changes to the DNA of the cancerous cells as it is possible to pinpoint the changes within each part of a tumour. Consequently, this requires the pathologist to understand genomic reports to carefully assess each part of a tumour, clearly describe germline changes, and therefore direct treatment options most suited to the patient's specific cancer. This is not without difficulty as although multiple mutations may be identified, it is tough to decipher which mutations are influencing metastatic and proliferative actions[9].

Pathologists will be involved in genomic studies of patients to assist in the early detection of cancer, or in its recurrence[10]. This may increase workload for the pathology department; with exact DNA information provided by genomic studies, expert knowledge on the resulting tumour's phenotype will still be required[11].

Genomics requires significant changes to the gathering and processing of pathological specimens. Sequencing of tumours requires specimens to be freshly frozen as opposed to formalin preservation - a significant shift in itself - as formalin destroys DNA[12]. Processing procedures will need to take into consideration that multiple sections of tumours will need to be sequenced as they may have insufficient DNA, multiple mutations depending on the

tumours internal map, or in metastatic tumours, different DNA mutations from the principal tumour[13,14]. Furthermore, a non-cancerous sequence is required to compare patients results to the normal functioning cell.

Genomics should be considered a powerful investigative tool. It is particularly useful in the study of rare diseases where there is a complex genetic component, and a single genetic mutation won't be predictive of disease. The broader approach provided by NGS is more likely to find a diagnosis. Genomics studies have begun to enhance definitive diagnosis for rare diseases[15]. This has resulted in much quicker diagnoses for up to 7% of the U.K. population which previously would have taken many years and multiple misdiagnoses to ascertain a definitive disease. The 100,000 Genome's Project generated a diagnosis for 15% of patients who previously had no diagnosis for their rare disease[5]. This has resulted in improved patient care as specific, tailored treatments can now be delivered to these patients in a timelier fashion. As more genomic studies are carried out, more causal relationships will be identified and further disease states mapped genomically[12].

The U.K. has introduced WGS to assist in the day-to-day diagnosis, treatment and monitoring of tuberculosis[3]. Pathogen genomics identifies pathogen susceptibilities and resistance. It is being used to prevent overtreatment in infectious diseases with testing trialled in *Escherichia coli, Neisseria gonorrhoeae* and *Clostridium difficile*[16]. This will ensure that patients are being given targeted treatment, minimising the need for repetitive courses of antibiotics. Building upon this, the field of pharmacogenomics - developing medicines and targeting diseases based upon genomic susceptibilities – has developed treatments such as cholesterol lowering antibody drugs[17] and anti-sclerostin antibodies for osteopenia[18]. Further developments are headed in the use of licenced drugs to treat diseases other than their original intention[15]. Known as precision medicine, this approach has been shown to be effective in refining dosing for warfarin, codeine and simvastatin by identifying mutations responsible for metabolism[19].

Ethical and societal dilemmas are created with the greater use of genomics in practice. Initial thoughts turn to the safe storage of sensitive information about vast numbers of the population, or potentially everybody if a WGS is derived at birth. This in itself poses a question – if a child is identified with an adult onset mutation that carries a significant risk to their life, how should this information be managed? Furthermore, if a genetic disease is identified in a family, which other family members should be informed of this increased risk? Will detailed knowledge of one's genome impact insurance? These are all points discussed currently before undergoing WGS and may be of significant concern to patients[15,20]. It is important to note that advances in genomics may be at a pace greater than patients understanding, and as partners in their care, we are responsible for providing comprehensible information[21].

Genomics is still very much evolving. Whilst some uses have been embraced, the field is only at the beginning of its potential application. Introduction will require substantial change to how pathology departments function and how patients travel through the health service, most notably in oncology services. As more information is generated and shared, more advances will be produced.

References

1. The Royal College of Pathologists. Genomics in medicine [Internet]. 2019.
2. Turnbull C, Scott RH, Thomas E, Jones L, Murugaesu N, Pretty FB, et al. The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. BMJ. 2018 Apr 24;361:k1687.
3. Torjesen I. Genomics-an aid to diagnosis not a replacement. BMJ. 2018 Mar 23;360:k1267.
4. Brittain HK, Scott R, Thomas E. The rise of the genome and personalised medicine. Clin Med. 2017 Dec 1;17(6):545–51.
5. The NIHR BioResource. Whole-genome sequencing of rare disease patients in a national healthcare system. bioRxiv. 2019 Jan 1;507244.
6. Sun L, Pfeifer JD. Pitfalls in molecular diagnostics. Semin Diagn Pathol. 2019 Sep;36(5):342–54.
7. Narayanan Murugesan S, Singh Yadav B, Kumar Maurya P, Chaudhary A, Singh S, Mani A. Expression and network analysis of YBX1 interactors for identification of new drug targets in lung adenocarcinoma. J Genomics. 2018;6:103–12.
8. Ramos-Vara JA, Miller MA. When Tissue Antigens and Antibodies Get Along. Vet Pathol. 2014 Jan 15;51(1):42–87.
9. Young AL, Challen GA, Birmann BM, Druley TE. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. Nat Commun. 2016 Nov 22;7(1):12484.
10. Hill S. Introducing genomics into cancer care. Br J Surg. 2018 Jan 1;105(2):e14–5.
11. Cho J, Ahn S, Son D, Kim NK, Lee K, Kim S, et al. Bridging genomics and phenomics of gastric carcinoma. Int J Cancer. 2019 Nov 18;145(9):2407–17.
12. Manolio TA, Abramowicz M, Al-Mulla F, Anderson W, Balling R, Berger AC, et al. Global implementation of genomic medicine: We are not alone. Sci Transl Med. 2015 Jun 3;7(290):290ps13.
13. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA, Kinzler KW. Cancer genome landscapes. Science. 2013 Mar 29;339(6127):1546–58.
14. Goswami RS, Luthra R, Singh RR, Patel KP, Routbort MJ, Aldape KD, et al. Identification of Factors Affecting the Success of Next-Generation Sequencing Testing in Solid Tumors. Am J Clin Pathol. 2016 Feb 1;145(2):222–37.
15. Chief Medical Officer of England. Annual Report of the Chief Medical Officer 2016 Generation Genome. 2016.
16. Cabibbe AM, Walker TM, Niemann S, Cirillo DM. Whole genome sequencing of Mycobacterium tuberculosis. Eur Respir J. 2018 Sep 12;52(5):1801163.
17. Nozue T. Lipid Lowering Therapy and Circulating PCSK9 Concentration. J Atheroscler Thromb. 2017 Sep 1;24(9):895–907.
18. Yavropoulou M, Xygonakis C, Lolou M, Karadimou F, Yovos J. The sclerostin story: From human genetics to the development of novel anabolic treatment for osteoporosis. Hormones. 2014 Dec 9;13(4):323–37.
19. Relling M V., Evans WE. Pharmacogenomics in the clinic. Nature. 2015 Oct 14;526(7573):343–50.
20. Morash M, Mitchell H, Beltran H, Elemento O, Pathak J. The Role of Next-Generation Sequencing in Precision Medicine: A Review of Outcomes in Oncology. J Pers Med. 2018 Sep 17;8(3):30.
21. Parry V, Middleton A. Socialising the genome. Lancet (London, England). 2017 Apr 22;389(10079):1603–4.