Olivia Jackson

How can genomics inform and shape future therapeutics?

Introduction

Genomics is the scientific field associated with studying the structure and function of the genome. In healthcare this knowledge can be used to inform our understanding of diseases and their treatment. Since the structure of DNA was discovered in 1953 by Watson and Crick[1], the field has expanded exponentially. This includes the sequencing of the whole human genome in 2003[2] and completion of data collection for the 100,000 Genomes Project in 2018[3]. Knowledge of the genome has already enabled the development of targeted therapeutics for malignancies[4] and genetic diseases[5], improving outcomes and reducing adverse effects[6]. Genomics will continue to have a significant impact and underpins personalised medicine, which is the future of healthcare. This is recognised by both the government and the National Health Service (NHS), whose goal of sequencing 500,000 genomes was realised in November this year[7]. In the following essay, the potential ways genomics may inform, and shape therapeutics will be discussed with a focus on cancer, rare and inherited diseases, pharmacogenomics, and infectious disease. In addition, some of the challenges to be overcome will also be covered.

Cancer

Cancer is caused by inherited or acquired DNA mutations. Genomics is therefore critical to understanding the treatment of this disease. Targeted treatments against specific mutations already exist, for example the use of Imatinib against *BRCA* mutations[8]. Utilising the mutations in a cancer cell to create targeted therapies is an example of precision medicine. This approach leads to fewer side effects as the characteristics targeted by the therapeutic are not found in normal cells[9]. This makes the therapeutic more palatable to patients and can improve compliance and outcomes[10]. As sequencing technologies advance and become cheaper, it will be possible to sequence all cancer patients' genomes. This will allow the discovery of new targets, the development of targeted treatments and a shift away from the more traditional and damaging chemotherapy approach.

Genomic information may also be used to stratify cancer patients. This is useful in deciding effective treatment options and investigating cancers of unknown primary (CUP). In

these cases, the molecular profile of the cancer may provide clues of its origin, or at the least mutations which may be targeted[11]. CUPs tend to have poor survival rates[11] in part due to the lack of knowledge of which drugs will be effective. Therefore, the use of genomics to guide therapeutic choice could have a significant impact in this area. Stratification can also be used to quantify risk[12]. This can allow prophylactic intervention (e.g. mastectomies), or earlier detection. This allows the most effective treatment option to be given sooner thus improving its efficacy and increasing the patient's chance of survival. An example of this is colon cancer, where survival rates for early-stage are greater than 90%. However, this falls to under 15% for late-stage[13].

Finally, through the analysis of circulating tumour DNA (ctDNA), genomics may be used to determine response to treatment and detect disease relapse[14]. ctDNA is released from dying tumour cells and detected in a patient's blood stream using DNA sequencing techniques. As cancer cells have a unique genomic profile, ctDNA can be used to quantify response to a particular treatment and guide treatment options. As ctDNA can be detected months prior to symptoms onset, it may also be a useful, non-invasive tool for monitoring for relapse, leading to therapeutics being started earlier and improving outcomes[14].

Rare and inherited diseases

Whilst individually rare, collectively ~7% of the population are affected by a rare disease in their lifetime and 80% of these have a genetic component[15]. Due to the rarity of these conditions, screening tests are often not available and or only look at specific changes. This results in a lengthy, often unsuccessful, diagnosis timeline, at the end of which patients have missed key timeframes for treatments[16]. In 2018 it was estimated that this diagnosis process had cost NHS England over £3.4 billion over 10 years[16]. Whole genome sequencing (WGS) could be used to detect many of these mutations in a much shorter timeframe.[17] Not only would this provide patients with an answer, but it will also inform therapeutic decision-making and, potentially, targeted therapies. With earlier diagnosis comes earlier intervention, which may help slow or prevent disease progression, potentially saving up to $500,000 per patient[18].

Targeted therapies have already been developed for some common inherited diseases such as cystic fibrosis[19]. These drugs can work in different ways including using gene editing to correct mutations, replacing sections of mutated DNA with a non-mutated section,

and supplying additional genetic material to compensate for non-functional mutated section[5]. As more genomic data is sequenced, it will become cheaper and easier to develop these drugs. Though it will take time until such therapies are common, this will have a significant impact on the quality and life expectancy of patients. A recent example of this is Casgevy, a gene-editing therapy licensed for the treatment of Sickle Cell disease, which was found to prevent 'severe pain crises for at least 12 months after treatment' in 97% of patients[20]. If used in conjunction with non-invasive prenatal testing, it may even be possible to cure these diseases in utero using gene therapy.[21] However, it should be noted there are significant ethical implications associated with this[22].

Pharmacogenomics

Pharmacogenomics is the study of how genomic variation alters drug efficacy and the risk of adverse reactions (AR). This feeds into rational prescribing; the idea that a one-size-fits-all approach to therapeutics is incorrect, and both drug choice and dosage should be tailored to the individual. This approach aims to prevent AR and the associated health and cost implications. Rational prescribing has been investigated for some drugs, for example testing for variants in the gene *TPMT* before prescribing Azathioprine for autoimmune conditions, but is not yet widespread[23]. This is despite it being long recognised that variants in key drug metabolism genes (e.g. CYP2C) are common and linked to significant AR[24]. These variations may affect either the pharmacokinetics or pharmacodynamics of a drug, with the impact on metabolism being a key focus. An example is the variant CYP2C9*3 which leads to patients being hypo-metabolizers of warfarin. This results in toxic concentrations of warfarin and a prolonged bleeding time[24]. AR to prescribed medications are responsible for 6.5% of hospitalizations[25]. This, combined with the 15% of patients who suffer an AR during hospitilisation[26], is estimated to cost £466 million[25] and results in 8000 overnight hospital stays[26]. As such, pharmacogenomics is clearly an important area to focus on to promote patient wellbeing and reduce costs.

Genomic data can be used to stratify patients and inform therapeutics choice, leading to a personalized approach for each individual. This reduces the trial-and-error aspect of prescribing and leads to more effective treatment, helping reduce the burden on the NHS. A greater understanding of how these variants impact drug efficacy may also lead

to the development of new drugs which either aren't affected by the variants or are tailored specifically to them[27].

Infectious diseases

Genomics can be used to analyse the genomes of pathogens, elucidating their lifecycle and mechanism of disease. This enables the identification of new drug targets and the development of new therapeutics and vaccines[28]. This is particularly useful in rapidly mutating viruses, such as Ebola[29], where genomics can be used to identify targets which pre-existing drugs will be effective against. Ultimately, this will lead to faster intervention and improved outcomes.

Genomics can also help us better understand how pathogens develop drug resistance. With this information, new drugs can be developed to overcome this[30]. It's been estimated that healthcare-associated infections cost the NHS £2 billion annually[31]. A small minority of the causative bacteria are responsible for much of the antimicrobial resistance burden[32,33]. Therefore, it is vital that solutions to their resistance are developed before prevalence of these bacteria increases.

The analysis of patients' genomes can help explain why some patients are more susceptible to infectious disease and have worse outcomes. An example of this is an ongoing study into patients' response to COVID-19 infection, which hopes to understand why some patients required intensive care when others didn't[34]. With this knowledge, patients who are more at risk can be identified, and depending on the disease, may be given prophylactic treatment. In addition, by identifying genetic causes of increased susceptibility, new therapeutics may be developed to help make up for the deficiencies in some individuals response to infection.

Prevention

Genomics may also help prevent and treat common diseases. All diseases have a genetic component influencing the risk of developing the condition, often through the interplay of several different genes with the environment[35]. Millions of variants can be analysed to calculate a polygenic risk score for diseases such as diabetes and heart disease[36]. Patients can then be stratified based on their risk. Used in conjunction with rational prescribing, this can lead to therapeutic interventions being given earlier before symptoms develop. In this

way, disease onset may be slowed or prevented. This may be particularly useful in reducing the prevalence, and therefore cost, of common diseases with multisystem complications. For example, in the UK 4.3 million people are diabetic[37], and the NHS spends around £10billion annually on their care[38].

Challenges

Several challenges must be overcome before the use of genomics in therapeutics can become common place; some of these are discussed below.

Cost poses a significant challenge. Whilst the cost of WGS is gradually decreasing[39], it is still prohibitively expensive to undertake on the whole population. This is on top of other costs, including drug development, clinical trials and training more bioinformaticians[26]. While several cost-effectiveness studies have been completed for rational prescribing[40,41], these often do not include the initial cost of clinical trials. Additionally, incentives may be required to induce pharmaceutical companies to research therapeutics for rare diseases, due to the financial return being lower[42.]

Another challenge is the lack of data available. The small population size of those with a rare disease can make identifying variants difficult. In contrast, common diseases have large populations, however the genetic variants often have a smaller impact, meaning more data is required for significant findings. Whilst the UK achieved its goal of sequencing 500,000 genomes this year[7], it will take a significant amount of time for this data to be analyzed, meaning it could be years before findings can be acted on.

The infrastructure and data storage required for implementing genomics throughout the healthcare system also poses a problem[40]. The NHS is in a better position than most due to the 100,000 Genome Project and the creation of Genomics England. However, a great deal of investment, time and resources would be needed to increase the capacity of the current infrastructure.

Another potential issue for rational prescribing is the attitude of healthcare professionals. Education on its benefits may be required to persuade them to utilize genomic information[40]. On top of this, the prescribing guidelines set out by the National Institute for Health and Care Excellence would need to be altered to include guidance on genomics. Without this, practitioners may be reluctant to adopt a rational prescribing approach for fear of breaking these.

Finally, it's important to appreciate that genomics is part of a larger picture, with environmental factors, epigenetics and transcriptomics all interacting to impact disease progression[43]. To develop the most effective therapeutics, all this data must be assimilated. A potential solution for this is the use of Artificial Intelligence (AI), which could assess all the data available and recommend the best outcome[44]. However, the AI would require large amounts of data to have been fed to it before it could make these decisions and would require a significant investment.

Conclusion

In conclusion, genomics can inform and shape therapeutics in several ways, some of which have already begun to be demonstrated. In this way, genomics could have a significant impact on healthcare in the future, becoming the foundation of therapeutics for many conditions, and paving the way for personalised medicine. However, significant challenges need to be overcome first, and substantial investments of time and money will be required before this can be achieved.

References

1. Watson, J., Crick, F. Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid. *Nature*. 1953; 171:737–738
2. International Human Genome Sequencing Consortium. Finishing the euchromatic sequence of the human genome. *Nature*. 2004; 431: 931–945
3. 100,000 Genomes Project [Internet]. Genomics England. 2023 [cited 20 December 2023]. Available from: https://www.genomicsengland.co.uk/initiatives/100000-genomes-project
4. Berger, M.F., Mardis, E.R. The emerging clinical relevance of genomics in cancer medicine. *Nat Rev Clin Oncol*. 2018; 15: 353–365
5. Roth T.L., Marson A. Genetic Disease and Therapy. *Annual Review of Pathology: Mechanisms of* disease. 2021; 16(1): 145-166 (2021)
6. McCormick, K.A., Calzone K.A. The impact of genomics on health outcomes, quality, and safety. *Nurse Manage*. 2016; 47(4): 23-26
7. Callaway E. World's biggest set of human genome sequences opens to scientists. Nature [Internet]. 2023 November 30 [cited 20 December 2023] Available from: https://www.nature.com/articles/d41586-023-03763-3#:~:text=30%20November%202023-,World%27s%20biggest%20set%20of%20human%20genome%20sequences%20opens%20to%20scientists,code%20for%20links%20to%20disease.&text=The%20world%27s%20largest%20collection%20of%20full%20human%20genomes%20has%20just%20gone%20live
8. Bhamidipati, D., Haro-Silerio, J.I., Yap, T.A. *et al.* PARP inhibitors: enhancing efficacy through rational combinations. *Br J Cancer*. 2023: 129: 904–916
9. Cancer Genomics Overview [Internet]. National Cancer Institute Center for Cancer Genomics. 2023 [cited 20 December 2023]. Available from: https://www.cancer.gov/ccg/research/cancer-genomics-overview#:~:text=Using%20the%20genetic%20changes%20in,is%20known%20as%20precision%20medicine.&text=Genomic%20information%20about%20cancer%20is,an%20approach%20called%20precision%20medicine.
10. Krzyszczyk P., Acevado A., Davidoff E.J. et al. The growing role of precision and personalized medicine for cancer treatment. *Technology (Singap World Sci)*. 2018; 6(3-4):79-100
11. Kato S., Alsafar, A., Walavalkar, V., Hainsworth, J., Kurzrock R. Cancer of Unkonw Primary in the Molecular Era. *Trends Cancer*. 2021; 7(5): 465-477
12. Kurian A.W., Antoniou A.C., Domchek S.M. Refining Breast Cancer Risk Stratification: Additional Genes, Additional Information. *Am Soc Clin Oncol Educ Book*. 2016; 35:44-56
13. Survival Rates for Colorectal Cancer [Internet]. American Cancer Society. 2023 [cited 20 December 2023]. Available from: https://www.cancer.org/cancer/types/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html
14. Cheng F., Su L., Qian C. Circulating tumor DNA: a promising biomarker in the liquid biopsy of cancer. *Oncotarget*. 2016; 7(30):48832-48841
15. Rare disease genomics [Internet]. Genomics England. 2023 [cited 20 December 2023]. Available from: https://www.genomicsengland.co.uk/genomic-medicine/understanding-genomics/rare-disease-genomics
16. Department of Health & Social Care. England Rare Diseases Action Plan 2022 [Internet]. 2022 February 28 [cited 20 December 2023]. Available from: https://www.gov.uk/government/publications/england-rare-diseases-action-plan-2022/england-rare-diseases-action-plan-2022#contents
17. Marwaha S., Knowles J.W., Ashley, E.A. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. *Genome Med*. 2022; 14, 23
18. EveryLife Foundation for Rare Diseases. The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study. 2023 September 14 [cited on 20 December 2023]. Available from: https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf
19. Lomunova M.A., Gershovich, P.M. Gene Therapy got Cystic Fibrosis: Recent Advances and Future Prospects. *Acta Naturae*. 2023; 15(2): 20-31
20. Medicine and Healthcare products Regulatory Agency. MHRA authorises world-first gene therapy that aims to cure si-ckle-cell disease and transfusion-dependent β-thalassemia [Internet]. 2023 November 16 [cited 20 December 2023]. Available from: https://www.gov.uk/government/news/mhra-

authorises-world-first-gene-therapy-that-aims-to-cure-sickle-cell-disease-and-transfusion-dependent-thalassemia
21. Chua P, Zhou S, Richmond M, Romano S. An Update on In Utero Gene Therapy for Cystic Fibrosis. Georgetown Medical Review. 2020;4(1).
22. Brown J.E.H., Koenig B.A. Ethical, Legal, and Social Implications of Fetal Gene Therapy. *Clin Obstet Gynecol*. 2021; 64(4): 933-940
23. Daniel LL, Dickson AL, Chung CP. Precision medicine for rheumatologists: lessons from the pharmacogenomics of azathioprine. Clin Rheumatol. 2021 Jan;40(1):65-734.
24. Goldstein J.A., Clinical Relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol*. 2001; 52(4): 349-355
25. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. BMJ 2004; 329: 15–19
26. McPherson A. Pharmacogenomics: a new normal for the NHS? - Genomics Education Programme [Internet]. Genomics Education Programme. 2021 [cited 20 December 2023]. Available from: https://www.genomicseducation.hee.nhs.uk/blog/pharmacogenomics-a-new-normal-for-the-nhs/
27. Oates J.T., Lopez D. Pharmacogenetics: An Important Part of Drug Development with A Focus on Its Application. *Int J Biomed Investig*. 2018; 1(2): 111
28. Sintchenko V., Timms, V., Sim, E. et al. Microbial Genomics as a Catalyst for Targeted Anttvirulence Therapeutics. *Front Med (Lausanne)*. 2021; 8: 641260
29. Martin S, Chiramel AI, Schmidt ML, Chen YC, Whitt N, Watt A, et al. A genome-wide siRNA screen identifies a druggable host pathway essential for the Ebola virus life cycle. *Genome Med*. 2018;10:58.
30. Jauneikaite E., Baker K.S., Nunn J.G. et al. Genomics for antimicrobial resisitance surveillance to support infection prevention and control in health-care facilities. *Harnessing Genomics for Antimicrobial Resistance Surveillance*. 2023; 4(12): E1040-12046
31. Guest J.F., Keating T., Gould D., Wigglesworth N. Modelling the annual NHS costs and outcomes attributable to healthcare-associated infections in England. *BMJ Open.* 2020; 10:e03336
32. Mustapha M.M., Srinivasa V.R., Griffith M.P., et al. Genomic diversity of hospital-acquired infections revealed through prospective whole-genome sequencing-based surveillance. *mSystems.* 2022; 7:e0138421
33. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet.* 2022; 399: 629-655
34. COVID-19 Study [Internet]. Genomics England. 2023 [cited 20 December 2023]. Available from: https://www.genomicsengland.co.uk/initiatives/covid-19
35. Jackson M. Marks L., May G.H.W., Wilson J.B. The genetic basis of disease. *Essays Biochem*. 2018; 62(5): 643-723
36. Lewis C.M., Vassps E. Polygenic risk scores: from research tools to clinical instruments. *Genome Medicine*. 2020; 12(44)
37. How many people in the UK have diabetes {Internet}. Diabetes UK. 2023. [cited 20 December 2023]. Available from: https://www.diabetes.org.uk/about-us/about-the-charity/our-strategy/statistics#:~:text=Our%20data%20shows%20that%20more,by%20148%2C591%20from%202020%2D2021.
38. NHS Prevention Programme cuts chances of Type 2 diabetes for thousnads [Internet]. NHS England, 2022. [cited 20 December 2023]. Available from: https://www.england.nhs.uk/2022/03/nhs-prevention-programme-cuts-chances-of-type-2-diabetes-for-thousands/#:~:text=Evidence%20has%20shown%20that%20the,effective%20in%20the%20long%2Dterm.
39. Mainstreaming whole genome sequencing: where are we now? [Internet] Genomics Education Programme. 2023. [cited 20 December 2023]. Available from: https://www.genomicseducation.hee.nhs.uk/blog/mainstreaming-whole-genome-sequencing-where-are-we-now/
40. Roden D.M., McLeod H.L., Relling M.V., et al. Pharmacogenomics. *The Lancet*, 2019;394(10197):521-532.
41. Berm EJJ, Looff MD, Wilffert B, Boersma C, Annemans L, Vegter S et al. Economic evaluations of pharmacogenetic and pharmacogenomic screening tests: a systematic review. second update of the literature. *PLoS ONE* 11(1), e0146262 (2016).

42. Zhao Z., Pei Z., Hu A., Zhang Y., Chen J. Analysis of Incentive Policies and Initiatives on Orpan Drug Development in China: Challenges, Reforms and Implications. *Orphanet Journal of Rare Diseases*. 2023; 18(220)
43. Olivier M, Asmis R, Hawkins GA, Howard TD, Cox LA. The Need for Multi-Omics Biomarker Signatures in Precision Medicine. Int J Mol Sci. 2019 Sep 26;20(19):4781. doi: 10.3390/ijms20194781. PMID: 31561483; PMCID: PMC6801754.
44. Primorac D, Bach-Rojecky L, Vađunec D, Juginović A, Žunić K, Matišić V et al. Pharmacogenomics at the center of precision medicine: challenges and perspective in an era of Big Data. Pharmacogenomics. 2020;21(2):141-156.