

Has the Human Genome Project Delivered for Healthcare?

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The Human Genome Project (HGP) was predicted to catapult medical research into the new millennium¹. The human genome is a sequence of bases encoding every gene in the body. The initial rewards have arisen from analysis of this data to determine the function of these genes², as well as deciphering genes arising from what was once thought of as 'junk' DNA.³ This has helped to establish the genetic basis of disease and then to inform novel approaches to drug design and treatment. This has yielded the concepts of genetic testing, gene therapy and pharmacogenomics – all have held much promise but have we begun to see actual clinical benefit?

Identifying Disease: Genetic Testing

Much of the benefit derived from genetic tests began long before the HGP got under a way. It was in the 1970s that newborn screening was established using Southern blot analysis; testing for phenylketonuria, for example, avoided detrimental effects to children's development simply with specialized diets.⁴ Not long after, in the early 1980s, PCR techniques enabled the development of tests for Cystic Fibrosis, Huntington's disease, and Duchenne muscular dystrophy.⁵ The further characterization of genes through the HGP has aided the development of more genetic tests; however, some of these are for very rare conditions, limiting their widespread benefit to healthcare. The HGP has helped to pioneer new techniques, helping to expand genetic testing, for example with pre-implantation genetic testing.⁶ More recently the Lancet has published results of the world's first bedside genetic test, which will be able to identify a particular allele in patients making them more susceptible to the adverse events of clopidogrel.⁷

Genetic testing does give rise to ethical issues that perhaps undermine its overall benefit. Should we be telling patients about their predisposition to a disease with an unpredictable course? The possibility of both type I and type II errors can also be detrimental – for this reason, counselling and informed consent is imperative. There is little doubt that genetic screening in many circumstances has improved clinical care but how much of that is due to the HGP can be debated.

Combating Disease: Gene Therapy

Gene therapy involves replacing disease-causing genes with functional copies.⁸ Gene therapy was first initiated in the early 1980s before the HGP was set up. However, techniques were cumbersome and yielded little success. The HGP, with its host of new DNA, certainly accelerated gene therapy and aided advancement in techniques for gene transfer. This still does not mean that technical difficulties have been avoided; the body has a tendency to mount an immune response against new DNA, and there is the risk of viral vectors reverting to their virulent form.⁹ In one case, gene therapy trials were

halted when two subjects with X-linked severe combined immune deficiency developed leukemia due to the insertion of a transgene next to an oncogene.¹⁰

As the HGP has aided discovery of genes for rarer conditions, some success stories have arisen, including a gene therapy trial for Leber's congenital amaurosis showing improvement in the sight of subjects.¹¹ There is also future promise with the recent development of nano-particles carrying tumour-destroying genes¹² and new viral vectors.¹³

China has been the first to approve commercial gene therapy products. 'Gendicine' and 'Oncorine' target the p53 tumour suppressor gene to aid tumour lysis.¹⁴ However, the tumour shrinkage seen has not necessarily translated to prolonged survival of cancer patients. Europe is also nearing the approval its first gene therapy drug 'Glybera' for the small population of patients with a lipoprotein lipase deficiency¹⁵.

The HGP has driven gene therapy trials forward, but this has not yet greatly influenced clinical practice and any successes have only been for rare conditions. The polygenic inheritance of common conditions such as heart disease or diabetes makes the success of gene therapy in the near future seem doubtful due to the complexity of targeting multiple erroneous genes.

Drug Design: Pharmacogenomics

It was predicted that the HGP would eventually reward clinical medicine with novel approaches to treatment. Pharmacogenomics is the concept that drugs can be tailored to an individual's genetic make-up to increase their efficacy and safety;¹⁶ for example by identifying how cytochrome P450 variants metabolise drugs differently.¹⁷ Patients could also benefit from speedier recoveries without having to pursue different treatment regimens before the best is discovered. In the future, warfarin dosing could become more precise by analyzing a patient's genetic variation in drug metabolism prior to administration, rather than using the currently unpredictable loading schedules.¹⁸ As for current clinical practice, it is now becoming more common to screen patients for thiopurine methyltransferase deficiencies before instigating azathioprine in rheumatology patients and those with inflammatory bowel disease.¹⁹ Patients with HIV can undergo assays to look for viral mutations that are causing resistance to their drugs, and subsequently be switched to a more effective regimen.²⁰ However, a problem arises if there are no adequate alternatives to prescribe for their condition.

Although the idea of personalized medication sounds exciting, in reality there are many more hurdles to jump before we fully enter this era. Drug companies may not find it profitable to fund the development of drug variants for small populations of patients. In everyday clinical practice, it may also be confusing to have variants of the same drugs, potentially giving rise to further prescribing errors. Finally, the actual decoding of the genome in relation to drug metabolism is not straightforward; there are multiple genes involved with many different polymorphisms to be analysed, which is likely to be time-consuming and costly.²¹

Conclusion

The decoding of the human genome was undoubtedly a major intellectual advance for mankind, however, the practical applications have not been as clear cut. Genetic testing has been well established into clinical practice. With earlier diagnoses aiding disease management, it will continue to have a positive influence as long as we don't succumb to superfluous testing. Gene therapy is showing promise, however, is still in very experimental phases. It is likely that we will soon start to see more gene therapeutics on the market but they may not translate to actual clinical benefit. Pharmacogenomics has already started to be used for management of certain conditions. However, I believe individually tailored medication for all conditions will remain a sci-fi concept for now. As a result, twenty years later we are still waiting for the HGP to impress.

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Conflicts of interest

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