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FACT SHEET – GENOMIC MEDICINE

Why sequence genomes for medicine?

Currently genome sequencing is expected to have the most impact in:

1. stratifying (better categorising) patients for appropriate cancer treatment
2. characterising and diagnosing genetic disease
3. providing information about an individual's likely response to treatment to reduce adverse drug reactions

See an expanded explanation of each area below.

1. Stratifying and treating cancer

A major focus of genomic medicine is cancer diagnosis and therapy. Clinicians can use an individual's genomic information to predict how their cancer will respond to drug therapy or surgery. In some cases, clinicians will profile the DNA and RNA of tumour cells to guide the use of existing treatments or focus on more targeted treatments.

Some patients have been spared costly and complex procedures based on a molecular diagnosis. Others have been spared severe toxicity from standard therapies.

Tumour development in a few patients has been stabilised – for a time, at least – by targeting specific molecules or pathways in the tumour cells. See the following examples:

Welch JS, Westervelt P, Ding L, Larson DE, Klco JM, Kulkarni S, et al. Use of whole-genome sequencing to diagnose a cryptic fusion oncogene. JAMA 2011;305(15):1577-1584.

Jones SJ, Laskin J, Li YY, Griffith OL, An J, Bilenky M, et al. Evolution of an adenocarcinoma in response to selection by targeted kinase inhibitors. Genome Biol. 2010;11(8):R82. doi: 10.1186/gb-2010-11-8-r82.

Australian Pancreatic Genome Initiative

Within Australia, useful information is being compiled by the Australian Pancreatic Cancer Genome Initiative (APGI), the Australian arm of an international consortium formed to catalogue the genetic changes of the 50 most common cancers.

Australia was tasked with cataloguing all the genetic changes in pancreatic cancer by analysing tumour samples from patients diagnosed with Pancreatic cancer.

A range of specialists - surgeons, pathologists, nurses - within APGI are undertaking this task, along with researchers in pancreatic cancer across the country. The ICGC initiative also includes significant contributions from 15 academic and clinical centres across the country and internationally.

2. Characterising and diagnosing inherited disease

Clinical genetic testing in Australia is primarily focused on diagnosing hereditary and rare genetic diseases. Every baby born in Australia is offered screening for approximately 30 genetic conditions (the Guthrie test) and more than 300 tests for genetic disorders are available through the healthcare system.

See: Royal College of Pathologists of Australia. RCPA Catalogue of Genetic Tests and Laboratories 2009. Available from http://genetictesting.rcpa.edu.au/

Clinicians worldwide are embracing genome sequencing to search for variants implicated in undiagnosed genetic diseases and using this information to guide treatment. In one of the most dramatic cases, a young boy underwent a risky, but seemingly successful, bone marrow transplant that was proposed in response to molecular data.

See: Johnson M, Gallagher K. One in a Billion: A Boy's Life, A Medical Mystery. JSOnline: Milkwaukee Wisconsin Journal Sentinel. December 25, 2010. Available from: http://www.jsonline.com/features/health/111224104.html

See other useful articles:

Bainbridge MN, Wiszniewski W, Murdock DR, Friedman J, Gonzaga-Jauregui C, Newsham I, et al. Whole-Genome Sequencing for Optimized Patient Management. Science Translational Medicine 2011;3(87): 87re83. doi: 10.1126/scitranslmed.3002243.

Worthey EA, Mayer AN, Syverson GD, Helbling D, Bonacci BB, Decker B,et al. Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. Genet Med. 2011:13(3):255-262.

Check Hayden E. Genome study solves twins' mystery condition. Nature 15 June 2011; doi:10.1038/news.2011.368. Available from: http://www.nature.com/news/2011/110615/full/news.2011.368.html

Incidence of inherited disease in Australia*

This table provides a summary of inherited diseases diagnosable by genetic testing. Testing for inherited disease is a critical step in the identification of possible treatments, and in the case of childhood diseases can provide critical advice and possible intervention in future reproductive choices.

Condition	Estimated frequency (2014)		
	Australia	NSW	Sydney
All births	306,329	99,260	76,069
Developmental delay	6,127	1,985	1,521
Rare genetic disease (<1/100,000)	4,595	1,489	1,141
Other genetic disorders			
Familial combined hyperlipidaemia	1,532	496	380
Familial hypercholsterolaemia	613	199	152
Dominant otosclerosis	306	99	76
Adult polycystic kidney disease	245	79	61

Multiple exostoses	153	50	38
Huntington's disease	153	50	38
Fragile X syndrome	153	50	38
Neurofibromatosis	123	40	30
Cystic fibrosis	123	40	30
Cardiomyopathies	123	40	30
Duchenne muscular dystrophy	92	30	23
Myotonic Dystrophy	61	20	15
Congenital spherocytosis	61	20	15
alpha-1-antitrypsin deficiency	61	20	15
X-linked ichthyosis	61	20	15
Polyposis coli	31	10	8
Phenylketonuria	31	10	8
Congenital adrenal hyperplasia	31	10	8
Spinal muscular atrophy	31	10	8
Sickle cell anaemia	31	10	8
Haemophilia A	31	10	8
beta-Thalassaemia	15	5	4
Becker muscular dystrophy	15	5	4
Total	**14,796**	**4,794**	**3,674**

*Source: Australian Institute of Health and Welfare 2012

Rather than sequencing the entire genome, rapid sequencing of only the protein-coding portion called the exome, can offer comparatively cost-effective analysis of many genetic disorders. Forms of inherited heart disease such as cardiomyopathies result from mutations in one of many different genes, and currently each one would need to be assessed individually to achieve a precise diagnosis. Similarly, severe eye diseases can result from a single mutation or a combination of many mutations.

Exome sequencing identifies any and all of the mutations in a single analysis, serving both as a diagnostic tool and a method to discover new genes and mutations that underlie these classes of disease. However, recent experience suggests that whole genome sequencing provides not only a more comprehensive picture of genomic rearrangements, particularly in cancer, but is also faster and more accurate in sequencing of exonic regions. It is expected that whole genome sequencing will quickly replace exome sequencing as sequencing costs decrease.

3. Predicting drug response and reducing adverse drug reactions

Equivalent Australian data is unavailable, but adverse drug reactions affect 1 in 5 outpatients and 1 in 11 inpatients and cost $80 billion per year in the US. Adverse drug reactions also result in ~100,000 deaths and 2.2 million severe repercussions in the US per year.

In Australia, the Therapeutic Goods Administration received 14,200 cases of severe adverse drug reaction in 2010. Up to 80% of adverse reactions are of unknown origin – thought to be mostly due to genetic differences in either the targets of the drugs or in the enzymes involved in their breakdown.

Currently, only a handful of DNA tests for variants implicated in drug metabolism have been recommended for use in Australia. The first of these approved in Australia was for the drug

abacavir, which is used to treat HIV infection, but causes a potentially life-threatening allergic reaction in 5-8% of patients.

See the National Health and Medical Research Council on the Clinical Utility of Personalised Medicine: http://www.nhmrc.gov.au/guidelines/publications/ps0001.

The number of recommended tests is expected to rise, as the US Food and Drug Administration list contains more than 100 drugs that mention specific markers that may change the way an individual responds:

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm