To what extent does Precision Medicine play a role in shaping the future diagnostics and treatment of Cystic Fibrosis?

By **Kalpa Chilukuru**

Introduction

Cystic fibrosis is a rare and genetic disorder (a mutation in the CFTR gene) affecting over 1 in 2500 Australians that clinicians are trying to treat using precision medicine.[1,2,3] The disease has no cure so far and only methods to control the symptoms.[4] The earlier the CFTR gene is detected and the earlier the patient is able to start targeted drug delivery, the better the chances are of reducing decline in lung function and other CF-related symptoms.

Precision Medicine

Precision Medicine (PM) is a customized treatment method determined by a patient's unique genotype, phenotype, disease state and many other factors.[5] "It's about customising medical decisions and treatments, tailoring them to a subgroup of patients, instead of a single individual (personalised medicine), or the traditional approach to medicine which is a one-drug-fits-all model for each disease".[6] "The main goal of precision medicine is to provide the right treatment at the right time to the right patients."[7] PM has the ability to accurately measure specific predictors of patient outcomes and can hence be implemented in personalized clinical care.[8]

Benefits

Benefits for a pharmaceutical or biotech company using PM is that they can have diagnostic or prognostic biomarkers to subcategorise patients for their likely response to a given drug. In clinical trials, this sub-categorisation increases the chances of success as it enables the drug to be trialled on a pre-selected population that is more likely to respond.[9] There are many examples where this approach showed that drugs that previously failed clinical trials when trialled against an unselected patient population of the disease, but later went on to be successful when the clinical trials were stratified to pre-select patients based on Precision Medicine and specific sub-category biomarkers.[10,11]

Challenges

The main challenge when developing a drug linked to a biomarker through Precision Medicine is that extremely detailed disease molecular phenotyping is needed. This needs to be repeated across multiple large cohorts of patients to ensure robustness.[12] It is often very expensive to generate this data and

requires careful clinical categorisation including genomic, transcriptomic, metabolomic analysis. The drug being developed either needs to change a biomarker response during treatment or be targeted at sub-categories of disease that have specific diagnostic or prognostic biomarkers. Precision Medicine adoption still needs awareness in medicine. Increased knowledge of the biomarkers and highly sophisticated diagnostic tests like Nextgen Sequencing tests (NGS) will be beneficial in improving the awareness of PM.[13]

Cystic Fibrosis

Cystic Fibrosis (CF) is the most common inherited lethal monogenic disorder resulting in a progressive pathology of severe damage to the lungs, intestinal tract, pancreas, and liver.[14] It is a recessive trait and only occurs when both the parents have 1 carrier Mutated CFTR gene (**Figure 1**). The Cystic Fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome 7 contains the instructions for making the CFTR protein. There are currently "2000 known mutations and 400 of which are disease-causing".[15,16] In people with CF, mutations in the CFTR gene cause the CFTR protein to malfunction creating a dysfunctional protein impacting chloride ion movement across cells and epithelial barriers.[17] This leads to an "imbalance of chloride and fluids resulting in build-up of thick mucus in various mucous producing organs". This results in persistent lung infections and, eventually, respiratory failure in the lungs, poor digestion, and problems in the reproductive system.[18,19]

Diagnostics

CF is more commonly diagnosed in babies. Newborns are diagnosed through routine screening, however, a proportion of patients do not exhibit symptoms or become diagnosed until adulthood.[20] In newborns screening a blood sample is checked for elevated levels of immunoreactive trypsinogen (IRT), which is released by the pancreas.If these levels are high, it is due to CF, babies being premature or having complications at birth. Therefore, other diagnostics are necessary to confirm CF.[21] Another diagnostic used is a sweat chloride test where pilocarpine is applied to an area of skin, sweat is collected to test the chloride level and if the level is above 60mM, it is likely the patient suffers from CF.[22] Some other diagnostics that have been approved for CF are Cystic Fibrosis carrier DNA sequencing and the forced expiratory volume (FEV1).FEV1 is a measurement of the amount of air the patient is able to force out in the first second of exhalation.This test is recognized as a predictor of the progression of lung diseases. A value of 10% or below the patient's baseline often indicates an infection or decline in the CF condition. It is expected that a person with CF will experience "a drop of 1-2% of their FEV1 each year due to the effects of lung damage".[23]

Treatment

Treatment of CF is highly intensive. CF speciality clinics involve treatment from nutritionists, physiotherapists, gastroenterologists, psychologists, endocrinologists to respiratory physicians.[24] A myriad of inhaled and oral antibiotics are given to CF patients for lung infections; nutritional additives to increase vitamins such as Aquadeks[25]; pancreatic enzyme replacements such as Creon to help digest dietary lipids for absorption; anti-inflammatory drugs like ibuprofen and drugs like Pulmozyme to break up the mucous build-up.[26]

CFTR modulators directly target the defective protein that is causing CF.The approved CFTR modulators include Kalydeco, Orkambi, and Symdeko.[27] In order to receive either of the CFTR modulators Orkambi or Symdeko, a CF patient must have a genetic test showing they have 2 copies of the mutations F508del and F508del homozygous.[28] Without this test result they will not receive the drugs. The latest and most effective of these drugs Trikafta is approved and used in the US and TGA safety approved in Australia but the Australian Pharmaceutical Benefits Scheme (PBS) has not yet agreed to subsidise the high cost of this medicine in Australia for CF patients. It can cost up to ~ $300,000 per patient per year.[29,30] CF patients are often on all these drugs at once and "the (drug) dose is adjusted, not only because of the patient's physiological characteristics, but considering the response to the enzyme, volume of food ingested, type of food ingested, number of meals, body mass gain, growth rate, and type of enzyme used".

Precision Medicine in Cystic Fibrosis

With DNA/Gene sequencing it is easier to understand whether specific mutations are causing a certain disease, enabling the researchers to identify what to target. In CF the drug exists but there is a lack of therapeutic efficacy.Another limiting factor is the high cost related to the diagnosis and application of Precision Medicine drugs.[31] Another factor considered is the need to expand medical education for the new era of genetics, with "broad knowledge of human genetic diversity and applicability in the treatment of CF."Gene therapy is the future of medicine, but much work is needed to apply this technology to more genetic diseases and make it more accessible to patients.[32]

In Precision Medicine, vectors are microscopic delivery vehicles that carry a healthy copy of a gene to the region of the body where the mutation needs to be corrected.[33] Gene therapy at Children's Medical Research Institute, NSW (CMRI) and

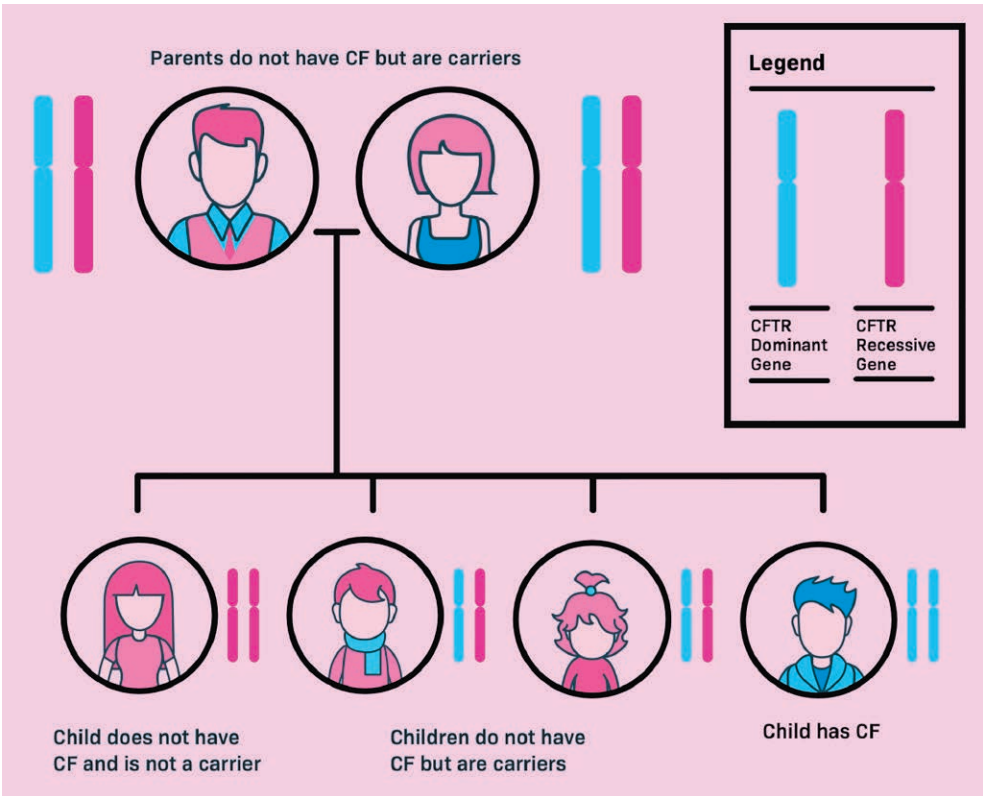

Figure 1: Cystic Fibrosis (CF) inheritance pattern

many other places around the world use 'AAV' vectors named after a harmless virus called Adeno-associated virus.[34] Once the vector to treat a specific condition is perfected in the lab, it is mass-produced for clinical trials.

Currently, Precision Medicine mainly encounters the difficulty of identifying the patient subgroups with lower incidence of certain genes.The match ratio is very low because there are too many mutations of pathogenic genes CF.[35] For Precision Medicine, molecular subtypes of patients with CF must be divided.[36] As a consequence, it is inevitable that there are only a small number of patients with a molecular subtype.Under this circumstance, the drugs selected are only applicable to this small proportion of people. Thus, costs are enormous and yields are extremely low.[37,38] Early detection techniques of the CF disease prognosis and research into genetic drivers will foster novel therapies; Early treatment is the key to minimizing lung function declines and other CF-related side effects.

Conclusion

Using Precision Medicine to diagnose and treat CF can improve disease detection, predict the susceptibility of treatment methods, customize disease-prevention strategies and prescribe more effective drugs.[39] The most researched method so far, Gene therapy works by fixing the error in the DNA. With a single injection, microscopic tools can scan the DNA, find the error, and correct it.Thousands of gene therapy clinical trials are happening all over the world, and some are having spectacular results, saving the lives of children and adults with serious genetic diseases.PM treatments have the potential to greatly extend life expectancy but are extremely expensive. Not all drugs work for every CF patient, therefore Precision Medicine will enable us to better tailor these medicines to get the most optimal results for each individual patient.[40,41,42] This is done by using tests to pre-identify what is the most efficacious drug for each individual rather than using trial and error in the clinic and years of waiting to tailor their optimal treatment.[43] Insufficient technologies, limited knowledge, and gaps in research are major obstacles to adding Precision Medicine to routine clinical care in the real world.

With Precision Medicine, researchers are now able to develop drugs using more defined targets, and physicians may use them to potentially target their patients' diseases.In spite of the massive amount of information that remains to be learned, Precision Medicine has improved the world of medicine. Many more human trials are being conducted to understand the effect of the drugs already created as well as new drugs being developed for CF. The ultimate goal of Precision Medicine in treating CF is to be able to use one drug to target all the different mutations of the CFTR gene.[44] JSPM

Acknowledgements

Since the concept of using precision medicine to treat cystic fibrosis is recent, reliable and credible information was acquired through an active collaboration with my mentor a Precision Medicine and cystic fibrosis expert Dr Kamala K Maddali[45]; She has guided me through the progression of this project and has provided her expertise. Many precision medicine and cystic fibrosis experts were interviewed in order to draw valid conclusions, this information is also supported by secondary sources such as books, scientific journals, websites, podcasts and videos, and ted talks.

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Kalpa Chilukuru is a high school junior studying in University Senior College, Australia. Her main interests lie in genomic medicine, neuropsychiatry and disease prevention. She develops her interests through mentored research projects and individual literature reviews. In the future, Kalpa aims to further her passion through a career in medicine, specializing as a clinical geneticist or a neurologist.

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