Thinking of the individual in rare disease clinical trials

Introduction

Rare diseases are often life altering and, in some cases, life-shortening, with most (69.9%) being first observed during childhood[1]. Although as a whole, rare diseases are fairly common (1 in every 17 people will have a rare disease)[2] each individual condition will have only a small number of people affected. This is a problem for traditional drug development approaches that rely on research in large numbers of people to produce medicines that are designed for the "average patient" in a one-size-fits-all-approach.

In recent years, there has been more hope as the need to give physicians bespoke treatment options has been acknowledged. Such personalized/precision approaches to medicine have become increasingly popular, especially in areas such as cancer [3]. These tailored approaches have changed drug development in many ways, but is it enough to translate this personalized drug development approach across for children with rare disease?

In this white paper we discuss the changes that personalized/precision medicine offer, the potential impacts and limitations on developing therapies in rare disease, and considerations for the future.

Personalized and precision medicine

Definitions by regulators and key research groups vary but, in general, personalized/ precision medicine means the tailoring of treatment based on people's genes, proteins, molecular structure and signaling pathways of their cells[4,5,6]. In its infancy stage, personalized medicine was intended to take advantage of the increase in knowledge about the genetic causes of disease, especially that gained from the Human Genome Project[7]. The terms 'Personalized' and 'Precision' became almost interchangeable in 2015 following the Obama administration's 215, million- dollar investment in the US "Precision Medicine Initiative"- a project which aimed to "arm Physicians with the tools they need to embrace new health and genetic technologies" allowing them to move away from "treating the average patient" to more personalized treatments[8].

Personalized/precision medicine has transformed drug development with the advent of large "data lakes", providing information from genetics to changes occurring in molecular profiles of disease (the so-called proteome, transcriptome, metabolome etc), and whole-scale epidemiology to profile illness in populations. This increased volume and detail of information allows researchers to move away from averaging across a whole population (aka the 'one-size-fits-all' approach), and instead subdivide information into smaller groups giving a greater level of precision.

However, outside the world of drug development, these personalized/ precision terms are either being used in a broader context ... or not used at all. The Personalized Medicine Coalition[9], representing key players such as physicians, patients, researchers, has sought to further define this emerging area:

> "Personalized medicine is an evolving field in which physicians use diagnostic tests to determine which medical treatments will work best for each patient or use medical interventions to alter molecular mechanisms that impact health. By combining data from diagnostic tests with an individual's medical history, circumstances and values, health care providers can develop targeted treatment and prevention plans with their patient[9]".

This is a far broader definition which begins to include more than the molecular and genetic profiles. It begins to describe how advancing science and data analytics allow us to more precisely group patients and conditions at a molecular level, whilst personalization links this to the patients' environment, lifestyle choices and values. But how much does this translate into the real-world understanding beyond coalitions of interested parties? We decided to test it out and canvassed a patient advocate with a rare condition as well as two health-care professionals unfamiliar with this debate. Figure 1 shows their responses in comparison to a summary of the established approaches described above.

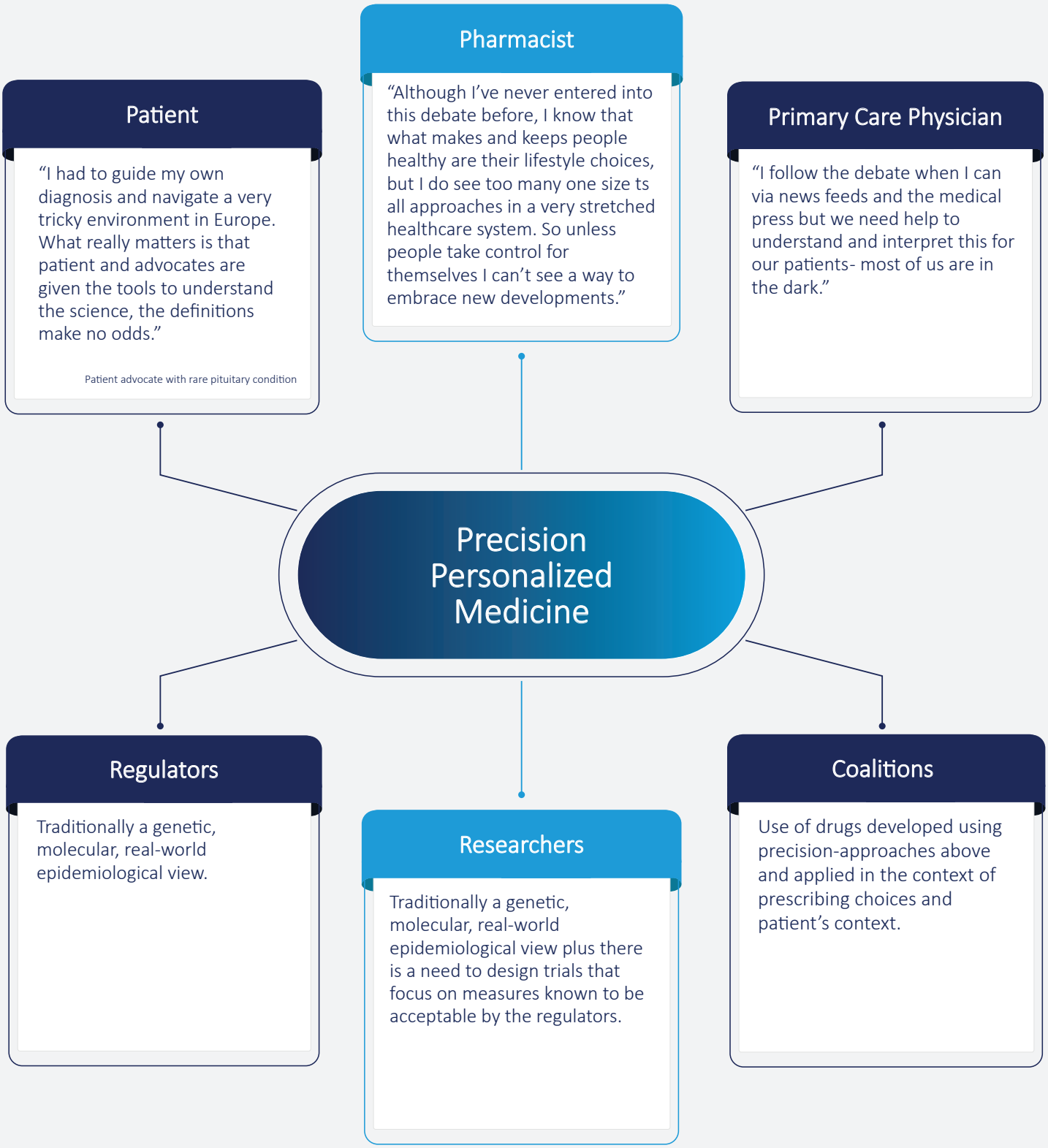

Figure 1: The varying meanings of precision and personalized in general drug development and medicine.

Clearly, even though the terms precision and personalized medicine are commonplace, we cannot assume that everyone has the same frame of reference and understanding of what precision means at the start. This can have impacts on the collaboration and execution efforts required for rare disease research.

Impact of personalized/precision medicine in rare disease

With approximately 80% of rare diseases having a genetic origin, an agreed definition of precision drug development techniques tailored to the rare disease in question would seem to be a perfect starting point for characterizing and treating people in such a small (tailored) group. Indeed, this knowledge ofthe genetics underpinning rare conditions is essential for the diagnosis of many conditions and designing the mechanism of action by which the therapies will work. However, using this as the backbone for the precision and personalization of trials is heavily reliant upon several key factors that are not optimized for rare disease populations (see Table 1).

	'Normal' precision medicine development	Rare disease medicine developments
Understanding the condition	Data-lakes can support this and help define groups of patients with similar disease characteristics who may respond to treatments in the same way.	Limited understanding of the condition due to low numbers of people affected. In addition, because many are chronically-developing diseases, how they affect someone's body will be different in each. They are not a selected sub-group of people from those diagnosed.
Conducting research	There are accepted things to measure to show benefit and people have been selected to be similar. This means that even with smaller groups, trials can usually be statistically powered using fairly traditional methods so that researchers have high confidence in results.	Very low numbers of people available for trials, all of which have been affected by the condition in a different way. There may not be agreement on what to measure, and there may not be consistency across these groups. All of these mean innovative statistical approaches need to be designed to have confidence.
Children and families	For many conditions children are involved after initial trials are complete and more is known. Also, as precision populations are grouped due to similar disease characteristic (e.g., a specific genetic or protein change) then treatment effects can be separated easier from the children's own growth and development rates.	The majority of research in rare disease is in children who have a chronic condition. Many may have developmental delays, some may have behavioural or psychological challenges as a result of their condition. All will have their own individual growth and development profile that will manifest over the months of studies needed.

Table 1: Comparison of key factors required for a genetic/molecular approach to personalized medicine drug development for general medicine vs rare disease.

Instead of subdividing a large population by characteristics to achieve precision/personalization (with these characteristics either being biological or due to the patient's themselves), for rare disease, especially in children where some of the most impactful research is undertaken, we must first start with the individual as shown in the examples.

Duchenne Muscular Dystrophy

The inclusion criteria for many trials involving children with Duchenne Muscular Dystrophy will often include a cut-off using a Performance Upper Limb (PUL) score. This is to try and include children in a trial who have similar stages of the disease. However, this condition affects each child differently and there is no known understanding of how the disease trajectory will play out. As the disease progresses, each child will lose particular functions at different times and to different extents naturally. Conversely, if a treatment is working, regaining function is also likely to have an unpredictable but individual profile. A standard set of inclusion criteria and standard set of endpoint measures are likely to only capture a very small amount of relevant information from these children.

Prader-Willi Syndrome

Prader-Willi syndrome is a rare genetic condition usually diagnosed shortly after birth. It is caused by errors in a group of genes on Chromosome 15 and results in a wide range of physical symptoms, learning difficulties, behavioural challenges, and the consequences effects on an area of the brain called the hypothalamus that produces hormones to regulate growth and appetite.

Someone with Prader-Willi is constantly hungry. People often end up being dangerously overweight due to an insatiable appetite that they can't quench. Behaviours such as stealing and hiding food to combat extreme hunger become the norm and many of the complications resulting from this condition are caused by obesity itself. Food security approaches, and their levels of success, affect weight increase enormously. For example, some families will lock cabinets in the house, some will make a schedule with the child to list when they will eat.

For clinical trials, it's not possible to standardise food security measures because each family and child will have a different food security/food seeking strategy that they're constantly trying to optimise. However, when it comes to measuring the effect of a drug on Prader-Willi disease, the variation in success of food security measures can influence standard endpoint measures, introducing a wide range of variability, and masking treatment effects. A more tailored approach is needed.

The main aims of drug development remain unchanged: researchers must show that the medicines work how they are designed to work; that they deliver a change that is meaningful both clinically and to patients and their families; and, that they improve quality of life. Rather, it's the starting point for designing a study to show tangible disease impact and patient benefit in involving children with rare disease that needs to be refreshed. **In rare, we need to design for the real-world from Day 1.**

Designing for real-world: finding commonality amongst individuals

It is impractical to design a drug for every individual and situation- the biology may not be understood well enough, or the disease may affect children in an inconsistent way so that unified treatment-responses are not possible. Therefore, research should focus on the commonalities that are found in what maximally informs care for rare disease children and their families.

For this, it is important to look through several different lenses and to clarify the knowns and unknowns. These include the considerations outlined in Figure 2.

What matters for children & families?

What matters most for maintaining their best quality of life? Covering all aspects beyond mechanism-of-action of the disease, e.g., social interaction, independence, behavioural support, and learning.

Individual disease profile

Understanding that loss of abilities due to a disease will vary in impact and timing depending on disease pattern and the child's growth and maturity rates.

Understanding current care pathways

Optimizing new therapies by learning from others- how have they had to adopt SoC so that it works for their child?

Improving data accuracy & relevance

Moving away from traditional hospital- to home-based testing provides a more natural environment for real-world evidence and removes confounding stress-related factors that unfamiliar environments can cause in children.

Figure 2: Looking through different lenses to understand the broader aspects of what a medicine needs to do and how this can be accurately measured to demonstrate benefit.

An example of this was observed by parents of children taking part in one of the earlier trials of Eteplirsen for Duchenne Muscular Dystrophy. The drug was considered to have 'failed' when prespecified changes in standard trial endpoints were not achieved. However, within this trial, children who had previously not been able to communicate what they wanted had started to be able to point, to smile, to interact with their family around them. Parents were moved so much that they approached the FDA themselves with video evidence of the drug's impact and a new trial was started.

Conclusion

Designing for the individual using specific knowledge of rare disease context is required to support real-world use and create transformative medicines for children with rare conditions. Collaboration is essential for the delivery of high-quality clinical trials. This means that regulators, researchers, the multidisciplinary care team, and especially patients and their families need to work together at the start of research to robustly identify the key decision points and disease manifestations that, if improved, will make the biggest difference. Together, a list of characteristics can be defined to show what improvement is, and then measured to demonstrate change that is both relevant and needed by the rare community.

Next whitepaper in the series:
Defining Success in Rare Disease Pediatric Trials

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