The mutual benefits of rare disease research and precision medicine

by Deborah Grainger, Ph.D

Precision medicine seems tailored to the study of rare diseases: at least 80 percent of them arise from genetic variations, and (though not always the case) show varying degrees of heterogeneity from patient to patient. They also represent a moderately untapped source of genomic ‘big data’, due to most being studied by only a handful of specialists worldwide. Now, many scientific establishments are recognizing the value of combining rare disease research data — not only for their collective potential to alleviate individual patient suffering, but as lenses to examine the more common diseases of man.

In modern research climates, where there is much emphasis on return of interest (ROI), a tendency to view rare disease research as beneficial to only a handful of individuals has endured. By definition, a rare disease is one that affects under 200,000 people in the United States, or under 5 in every 10,000 individuals in Europe. Given these numbers, it is easy to see why the classic, intractable logic predominates that fewer patients equal fewer global benefits — but is this prevailing logic inherently flawed?

“Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease.”

British Physician William Harvey, 1657
Looking at the bigger picture helps to broach potential answers to such a question... There are around 7,000 known rare diseases meaning that, in total, around 30 million Americans and a similar number of Europeans live with one of these conditions ‘making rare disease patients paradoxically common’. In fact, it is estimated that around 400 million people throughout the world suffer with a rare disease, meaning the collective disease burden of these conditions is comparable to more well-known counterparts.

Admittedly, rare diseases vary more in terms of symptoms, severity, and prognoses than major diseases such as cancer, but precision medicine is a great leveler, because of its approaches, we now understand that most cancers are as individual as their hosts — even those of the same type and stage show this variance. Yet, we still appreciate the translational benefits of studying cancers across the board, whilst simultaneously racing to identify more stratified treatments for them. The predominantly genetic nature of rare diseases, plus new technologies such as CRISPR-Cas9 gene editing, surely open up similar translational potential between remote diseases. Once one successful gene therapy becomes established, has a precedent not been set?

Perhaps the most compelling testament of the value of rare disease research though, especially in the context of counterbalancing a ROI-centered argument, is its past triumphs in wider knowledge acquisition. Ground gained in the research of a surprising number of rare diseases has uncovered some of the inner-most workings of the more common ones.

The study of Tangier disease for example—an extremely rare disease manifested by severe perturbations in cholesterol metabolism—may have identified a therapeutic target for mitigating the risk of heart disease; a receptor protein encoded by the ABCA1 gene. This protein interacts with the apoA-1 protein to clear excess cholesterol from the cell interior in the form of HDL (good cholesterol) for removal by the liver (2). Furthermore, it performs this same task in the brain, but instead binding a protein called ApoE—thus playing a role in the removal of amyloid-beta and, therefore, provides insight into Alzheimer’s disease (3).

Other notable examples include Liddle syndrome (a rare kidney disorder) and its contribution of knowledge on the pathology of hypertension (4) and Fanconi anemia, which has shed light on the intimate relationship between genetic instability and cancer (plus mechanisms of bone marrow failure and resistance to chemotherapy) (5).

More recently, the fatal disease Niemann-Pick Type C (NPC), has even helped us to understand how Ebola spreads throughout the body — the link being that the Ebola virus uses the NPC1 protein made by the gene to gain entry to the cell and replicate (6). Mice that only have one normal copy of the NPC gene — simulating carriers of the disease — have much higher Ebola survival rates (7). From the outset, would anyone have made this connection?

As the NPC-Ebola association demonstrates, scientific discoveries rarely start out at point ‘A’ and work directly to ‘B’ in a linear fashion. They normally get there via a handful of other letters (perhaps via ‘Z’, ‘F’ and ‘Q’ in the process). Widening the net to capture the entire alphabet and working to identify the unpredictable,by tracing emerging patterns is a smart strategy — especially if you have optimized, automated processes available to do so. This approach has been adopted by research organizations like Genomics England, which in 2014 got its 100,000 Genomes Project underway in a bid to sequence patient genomes to understand rare diseases better.

With more budgets being set aside for precision medicine, such as the $215 million recently dedicated by the US Government to the National Institute of Health’s Precision Medicine Initiative, it is only a matter of time before precision medicine enables more rare disease research success stories. Successes such as the repurposing of a failed cancer drug in the treatment of premature aging condition Hutchinson-Gilford Progeria Syndrome (9) — enabled by the landmark Human Genome Project and the identification of progeria’s underlying genetic causes.

Spurred on further by additional innovations in genomics, the falling cost of whole genome sequencing and data collection and sharing, the rare conditions that have borne the ‘orphan disease’ label for so long may yet reveal the secrets to some of Nature’s most unyielding mysteries. Fewer patients equal fewer global benefits! This old, persistent logic is, most likely, deeply flawed.

References