Establishing the prevalence of rare diseases from published literature

We are committed to bringing insight and high-quality solutions to our clients. In doing so we help them meet the many challenges of today's complex healthcare marketplace.

The valuation outputs we generate can be easily integrated with any in-house existing financial systems, presentation styles or platforms that may be currently operational. This ensures a faster uptake within the business, enabling resources to be re-directed towards implementing the outputs and leveraging new information.

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Why do we need to know the prevalence of rare diseases?

The focus of drug development has shifted in the last 10 years to treatment of rare diseases. This has largely been driven by the payer environment. Where markets have shifted towards value-based pricing it has been easier to establish a higher value for a medication in a rare disease space where there is no current effective standard of care than it has been to launch say the next generation of anti-hypertensive. Clinical trials in rare diseases tend to involve fewer patients and can be quicker to run (excluding recruitment challenges!) than a conventional 'big indication' trial where the trial needs to demonstrate increments on a relatively effective current standard of care.

According to the NIH, there are over 7,000 rare diseases (many being sub-sets of larger diseases), many of which have not been quantified to date. Traditionally, companies developing an asset would use prevalent population estimates in order to create a forecast to understand market potential and thus asset value. The eligible patient population is one of the single most significant drivers of a forecast and thus impacts the ultimate value estimate of a healthcare asset.

This lack of solid epidemiology data poses something of a problem when it comes to being able to value an asset for a rare disease.

So, what's the problem with rare diseases? Why are they any different to more frequent conditions?

Data regarding the frequency of rare diseases is somewhat lacking within the public domain. Since these diseases are so rare and there are so many of them, finding literature regarding prevalence becomes exponentially diminishing when compared with a disease such as, say, type 2 diabetes. The more frequent the occurrence of the disease, the more likely you are to be able to find data on it.

The other complication is that when you do finally find any data, it can be old, of limited quality or applicability or could relate to prevalence in a birth cohort rather than being a true estimate of disease prevalence in the whole population.

So, while there are many estimates of prevalence for diseases such as hypertension and diabetes, such estimates are not often readily available in the case of rare diseases.

And to add insult to injury, the names of these rare diseases may be different or there may be many names that all refer to the same condition (e.g. Frontotemporal lobar degeneration is also known as Picks disease or frontotemporal dementia). This can also vary by country – for Crohn's disease, a search of the literature will not turn up much for its prevalence in Germany, however a search for "Morbus Crohn" disease will.

Furthermore, since many rare diseases have a genetic basis, it is necessary to find country-specific estimates for any market or territory that you wish to understand market potential for, otherwise final prevalence predictions will have limited usability since the confidence in the numbers will be low.

These factors combine to make it increasingly difficult to generate robust, transparent and comparable data for use in asset valuations.

Can't I just use the stats I find on Orphanet?

While there are specific websites that contain content pertaining to rare diseases, these are often not 'policed' for validated in terms of their content. It is tempting to use an official website and the statistics reported therein, however, there is often little to not explanation of what the statistic relates to. For example, the website may state a frequency of 1 per 120,000, but with no explanation of what country this relates to, whether this is for the entire population, if this is incidence or prevalence or reflective of a birth cohort occurrence. There is often no time point (was this from the 1970's or more recent?), sample or screening criteria, or diagnostic criteria stated alongside the figure. It becomes difficult to impossible to be able to know how that figure can then be used to estimate a prevalent population since there is no information regarding what this number relates to and how it can be applied.

So how do you quantify a rare disease?

For quantification of rare diseases more time, patience and rigour is required to find usable source literature and statistics. Coupled with that, we need more in-depth models and methods to convert the data that we can find to a solid estimate of the prevalence of the

disease that we want to study. If this data is going to be part of a regulatory submission, then the explanation of the disease modelling also needs to be transparent and the sources need to be applicable and strong enough to justify the patient quantification estimates put forward.

Exhaustive search for any available data

Quantification for a rare disease should start in the same way as for any other disease – with an exhaustive search of the available literature. All terms used in the search should be captured so that it is clear that any and all names associated with the condition have been

sought during the initial collation of the data, and that suitable and relevant terms have been used.

Prevalence vs. Incidence

While searching for prevalence may not turn anything up (or possibly birth prevalence), searching for incidence may be more effective. For rare diseases it is often more common to find data reporting incidence of the condition rather than prevalence. Sometimes it is not readily apparent as to why this is, but sometimes this relates to life-expectancy – many rare diseases have a significantly limited life-expectancy. Often rare diseases are inherited conditions, therefore there is a focus on screening and detection in live births, hence reported birth-prevalence.

Life-expectancy and disease natural history

By combining different pieces of data regarding the disease, it is possible to model how the disease is likely to move through the population by age and over time. If we know how many

patients are being added to the pool in each year (our birth cohort number), we can model how we expect those patients to survive in each subsequent year and each incremental age cohort. This requires a little more data than just the incidence and life-expectancy, it should also incorporate the general reported back-ground mortality in a specific country population (by both age and gender since males and females have different survival profiles in the population, and this varies from country to country).

By combining all data that we have and building up a map of what the disease looks like, we can estimate what this would result in on the national scale of any country.

Impact of access to healthcare and new treatments

For rare diseases, the aim of most new treatments in development will be to extend survival with the disease. This will have a fundamental shift in terms of the working disease model and resulting prevalence figures since prevalence is directly equivalent to incidence x survival.

A significant factor to add to the mix is the overall access to healthcare and likely diagnosis of a rare disease. While this may be less of an immediate issue or concern in most western markets, it is a significant factor to include in less developed markets, even if there is significant prevalence of the condition. Questions to ask should include: are patients likely to be diagnosed? Are patients likely to receive or be able to afford treatment? Both of these factors should be included in any prevalence model, but also should be integral to any asset valuation consideration.

Sounds like this could take some time and I could get it wrong – can I just approach my usual epidemiology vendors for this kind of data and support?

The majority of companies that provide epidemiology data for commercial use have limited experience in quantification of rare diseases and models to translate data in to working, dynamic disease models capable of capturing drivers of disease and treatment impact. Most methods applied are static snapshots rather than true dynamic models where variables can change over time.

In addition, most epidemiologists, while they would be able to find relevant incidence / prevalence data in the literature do not often have the disease pathology perspective or clinical background to be able to comfortably predict and model impact of treatment on disease progression.

Black Swan Analysis and rare diseases

The Black Swan Analysis team provide a unique perspective for rare disease quantification, through the combination of traditional epidemiological methodology with pathology and clinical disease understanding plus advanced forecasting techniques.

Within the Epiomic™ database and series if reports, we have over 75 rare diseases and are building more each month for our clients on a custom basis. We have extensive experience in quantifying niche and rare diseases for asset valuations and forecasts as well as helping to prepare data for submission to regulatory bodies such as the FDA or EMA and responding to questions.

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