HOW COMMON IS RARE?

By Kate Grady, Sarah Hersh

Data from newborn screening reveals that rare diseases might be more common than we think.

As their name suggests, rare diseases affect small numbers of patients. Understanding the "true" number of individuals with a rare disease (both undiagnosed and diagnosed) is critical to many aspects of orphan drug development including:

- Regulatory qualification for orphan status (<200,000 in the US and <5 per 10,000 in Europe)
- Clinical development and the ability to power and recruit clinical trials
- Accurate forecasting
- Pricing and reimbursement negotiations

However, despite the importance of the size of a rare disease patient population, getting to the answer is challenging.

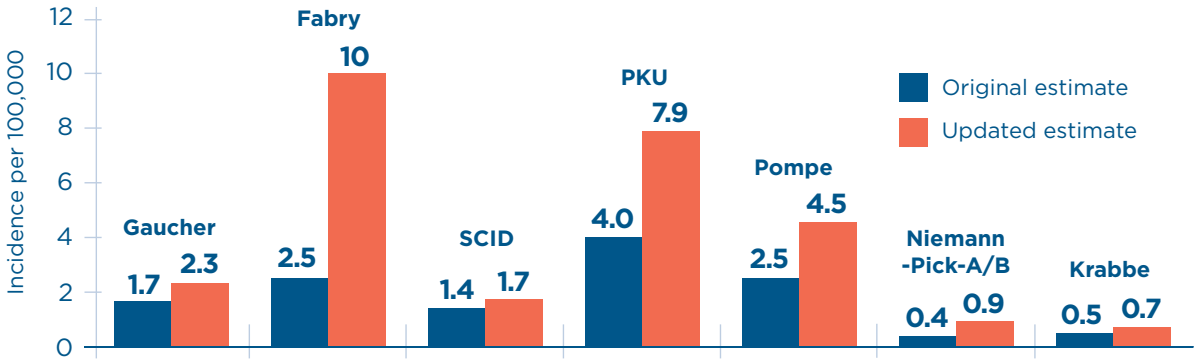
The first issue is lack of data, as published epidemiologic studies in rare diseases are often limited. When studies do exist, they may be impacted by the inherent methodologic difficultly of measuring small populations.

Publications prior to 2000 often rely on retrospective patient-based methodologies to extrapolate incidence rates. The fallacy of retrospective data is that by relying on clinical diagnosis it is easy to miss patients, and thus the incidence rate can easily be underreported. Other more recent methodologies, such as claims based analyses, can also be limited due to imperfect classification of rare diseases by ICD-10 codes.

Recent publications, however, have shown that newborn screening (NBS) has improved our ability to more accurately size rare disease patient populations by removing the necessity of clinical diagnosis.

When NBS studies are compared to retrospective studies for the same rare disease, the limitations of retrospective studies become evident. **Figure 1** shows the comparison of incidence rates based on older retrospective analyses vs. more recent newborn screening. **This analysis highlights that incidence rates have been under-estimated by 24% - 300%**. Thus, recent publications based on newborn screening make it clear that rare diseases may not be as rare as we once thought.

Figure 1. Change in incidence estimates over time



	Gaucher	Fabry	SCID	PKU	Pompe	Niemann -Pick-A/B	Krabbe
Percent Increase	**34%**	**300%**	**72%**	**97%**	**82%**	**140%**	**49%**
Original Estimate **Year(s)**	**1999**	**2001**	**1993**	**1999**	**1998**	**1999**	**1999**
Original Estimate **Population**	Australian	N/A	Swedish	N/A	American (NY)	Australian	Australian
Original Estimate **Methodology**	Retrospective Study	N/A	Population Survey	N/A	Population Survey, Carrier Screening	Retrospective Study	Retrospective Study
Updated Estimate **Year(s)**	**2017**	**2017**	**2016**	**2013**	**2017**	**2017**	**2017**
Updated Estimate **Population**	American (IL)	American (NY)	Swedish	American (National)	American (IL)	American (IL)	American (NY & MO)
Updated Estimate **Methodology**	NBS	NBS	NBS	NBS	NBS	NBS	NBS

Although newborn screening has mitigated some of the major methodologic limitations of studying rare diseases, challenges still exist:

1. **Variability still exists:** Different screening techniques and geographic variation due to genetic clustering can lead to variation in NBS estimates. For example, four recently published papers (2012 – 2016) on NBS in Pompe Disease result in an estimated range in incidence of 1/4,500 to 1/21,000.[2] The range in findings is hypothesized due to variation in the diagnostic methodology used as well as the populations sampled.

2. **Limitations of real world applicability:** While an updated incidence estimate may allow for more accurate patient projections, the feasibility of diagnosing these patients in a real-world setting is dependent on NBS implementation. Despite efforts to standardize, implementation of NBS is fragmented, with each US state and European country responsible for its own program.

This complex dynamic of increasing the accuracy of rare disease population sizing is highlighted through a SCID case study.

1 Early: JAMA. 1999 Jan 20;281(3):249-54.; Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Kinzler KE, Vogelstein B, eds. The Metabolic and Molecular Bases of Inherited Diseases. 8 ed. New York, NY: McGraw-Hill; 2001:3733-74.; Int. J. Neonatal Screen. 2017,3(2),11; Calif Med. 1971 Jul; 115(1): 42–57.; Am J Med Genet. 1998 Aug 27;79(1):69-72.
Late: J Pediatr. 2017 Nov;190:130-135.; Mol Genet Metab. 2016 Aug;118(4):304-9. JAMA. 2014 Aug 20;312(7):729-38.; Genetics in Medicine 15, 591–599; J Neurosci Res. 2016 Nov; 94(11): 1063–1075.
2 Elliott et al, 2016; Hopkins et al, 2015; Liao et al, 2014; Wittman, et al 2012

Case Example: Deep dive into severe combined immunodeficiency (SCID)

Primary immunodeficiencies are diseases resulting from inherited defects of the immune system.

SCID incidence estimates in the early 1990s suggest an incidence of ~1 patient per 100,000 newborns. The original methodology of the well-cited Swedish survey relied on physicians to report any established or suspected SCID cases during a six-year period.[3]

The Swedish publication went as far as to conclude that: 'certain syndromes are probably reported at close to 100% incidence . . . SCID is one such disease, and the estimated incidence of 1.4 cases per 100,000 newborns probably approximates the "true" number.'[4]

However, this confident conclusion was later contradicted by publications based on a pilot newborn screening program in Stockholm that found an implied incidence of ~1.7 cases per 100,000[5]. Thus, even after confidently claiming a near 100% diagnosis rate, newborn screening was able to identify patients with an implied incidence 25% higher than the previous estimate.

Conclusion

While NBS may not be the only factor in understanding the "true" number of rare disease patients, it has significantly improved the methodologic rigor with which we can begin to estimate patient numbers.

However, it is important to consider the following implications when pursing any rare disease opportunity:

1. **Careful consideration of the epidemiologic data:** Consider the importance of the study methodology, prioritize NBS studies over retrospective publications and triangulate disparate NBS estimates when multiple studies are available.

2. Understand the implications: Increasing the size of the patient population does not automatically result in an increase in the addressable population.

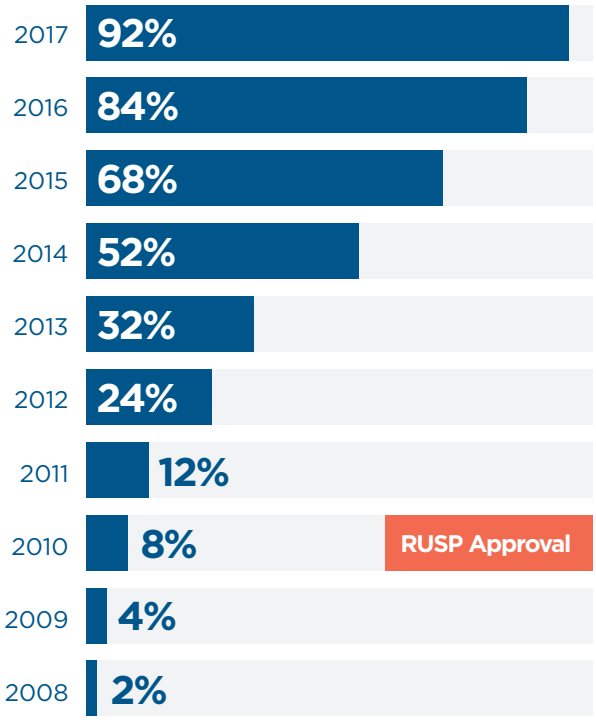
   Implications for Diagnosed Patients: Given the fragmented implementation of NBS adoption in both the US and EU, analogs suggest it may take more than ten years to screen the majority of newborns (see **figure 2**). This "ramp to peak diagnosis" should be considered as a major driver of any rare disease opportunity.

   Implications for Treated Patients: NBS creates a unique situation where pre-symptomatic patients are diagnosed, resulting in the clinical question, "When do you initiate treatment?" - a decision which is often further complicated by the cost of therapy. This dynamic requires physicians, patients / parents and payors to carefully determine the "right time to treat."

Newborn screening has provided an important means to better understand how big a very small population truly is. It has also raised important questions that should be considered when evaluating any rare disease opportunity.

3 J Clin Immunol. 1982 Apr;2(2):86-92. **4** Clin Immunol. 1982 Apr;2(2):86-92. **5** Int. J. Neonatal Screen. 2017,3(2),11

Figure 2. This graph demonstrates the adoption curve of state level NBS for SCID. In 2010, SCID was added to the US Recommended Uniform Screening Panel (RUSP). Each state is responsible for adopting the recommendation. In the example of SCID, Federally funded grants have assisted with SCID NBS implementation.[6,7]



In Huron's next whitepaper, we discuss how different predictive epidemiology and patient burden modeling can reduce uncertainty when launching new rare disease treatments and how to leverage these tools to seize future opportunities.

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6 https://www.aphl.org/programs/newborn_screening/Documents/2011SCID/Cuthbert-SCID-Overview.pdf#search=scid%20grant **7** Immune Deficiency Foundation, Accessed May 2018