The Good, the Bad and the Necessary in Rare Disease Studies

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Topics

- **The General Healthcare Landscape**
- **An Integrated Evidence Plan**
- **Current Trends and Challenges affecting Rare Disease**
- **Overcoming some of these challenges through the use of Real World Evidence**
- **Our experience and capabilities**

Global healthcare landscape

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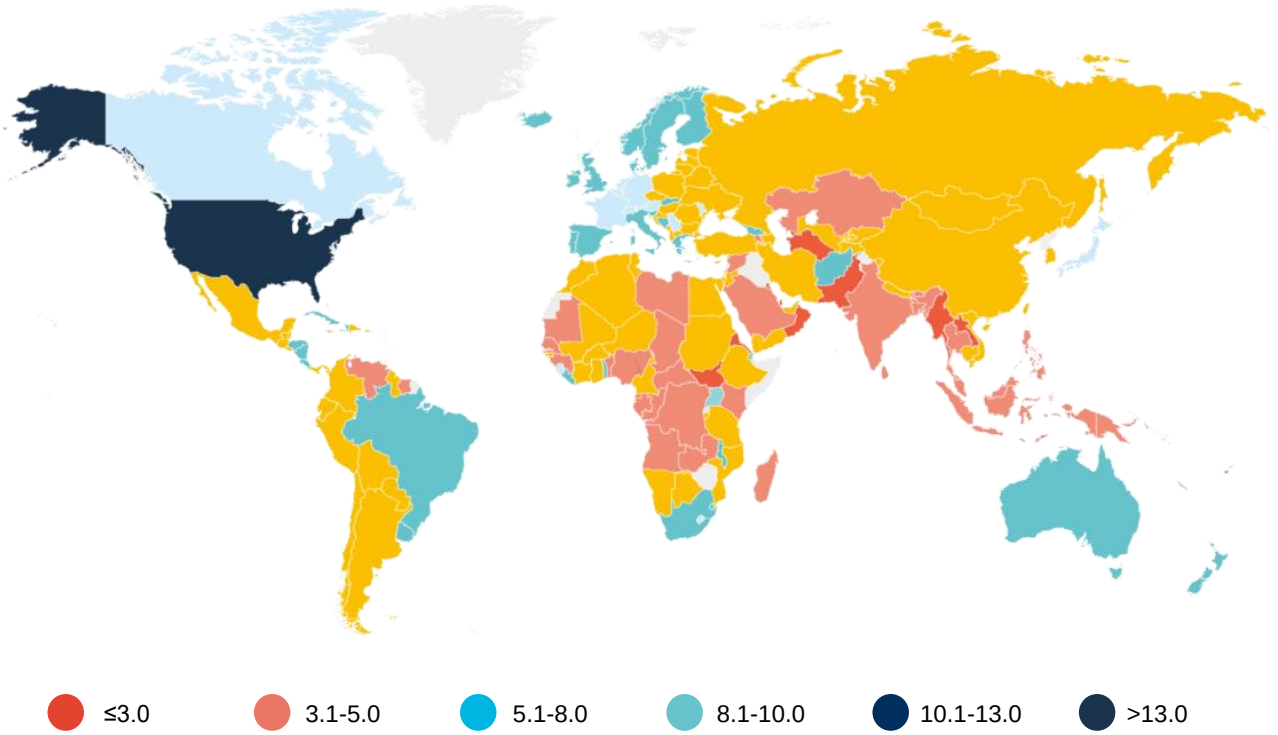
Global healthcare landscape

Global healthcare spend is increasing

Expenditure on Healthcare as a Percentage of GDP[1]



US Healthcare Spend = ~18% of GDP, but Pharmaceuticals <2%[2]

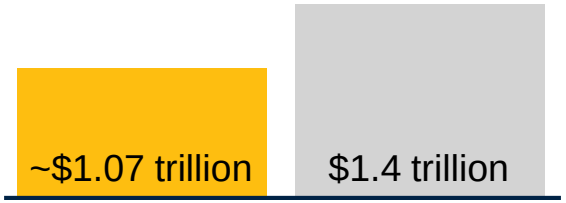
Global Health Observatory, World Health Organization, "Total expenditure on health as a percentage of the gross domestic product 2013," 20 Aug. 2015.
Centers for Medicare & Medicaid Spending, 2014

Global healthcare landscape in the Future

Looking ahead: Projections for 2020

Demand for **Real World Evidence** to support reimbursement and market access

Global spending on medicines



One medicine per person per day
World population

Next 5 years
225 new drugs coming to market with ~1/3 aimed at cancer

Governments and Healthcare Payors face cost and capacity challenges

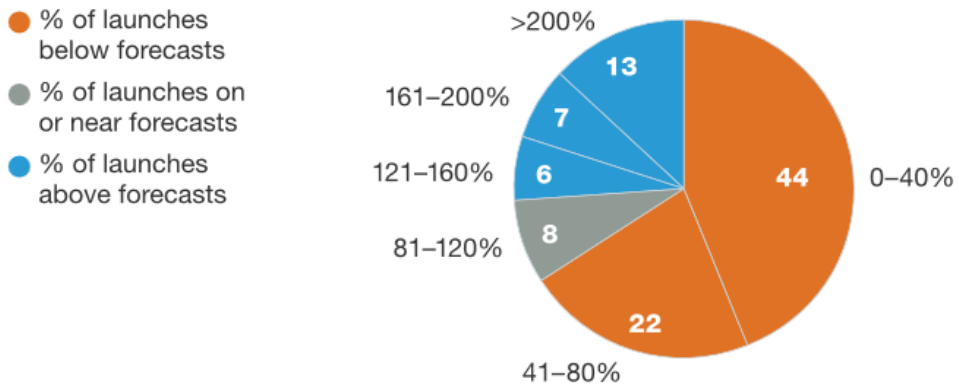
Inclusion of >Real World Evidence Data within drug development trials

- Source: “Global Medicines Use in 2020" report, IMS Institute for Healthcare Informatics, November 2015.

Most Drug Launches do not go to plan…..

Two-thirds of a sample group of drug launches failed to meet prelaunch sales expectations for their first year on the market.

Actual sales during first year of launch as % of forecast sales 1 year prior to launch[1]



Of launches that **exceeded** forecasts in year 1, **65%** continued to do so in year 2, and **53%** of those exceeded forecasts in year 3.

Of launches that **lagged** forecasts in year 1, **78%** continued to do so in year 2, and **70%** of those lagged forecasts in year 3.

[1]Sample comprises 210 new molecular entities launched between 2003 and 2009 for which consensus forecasts were available from Evaluate 1 year prior to launch.

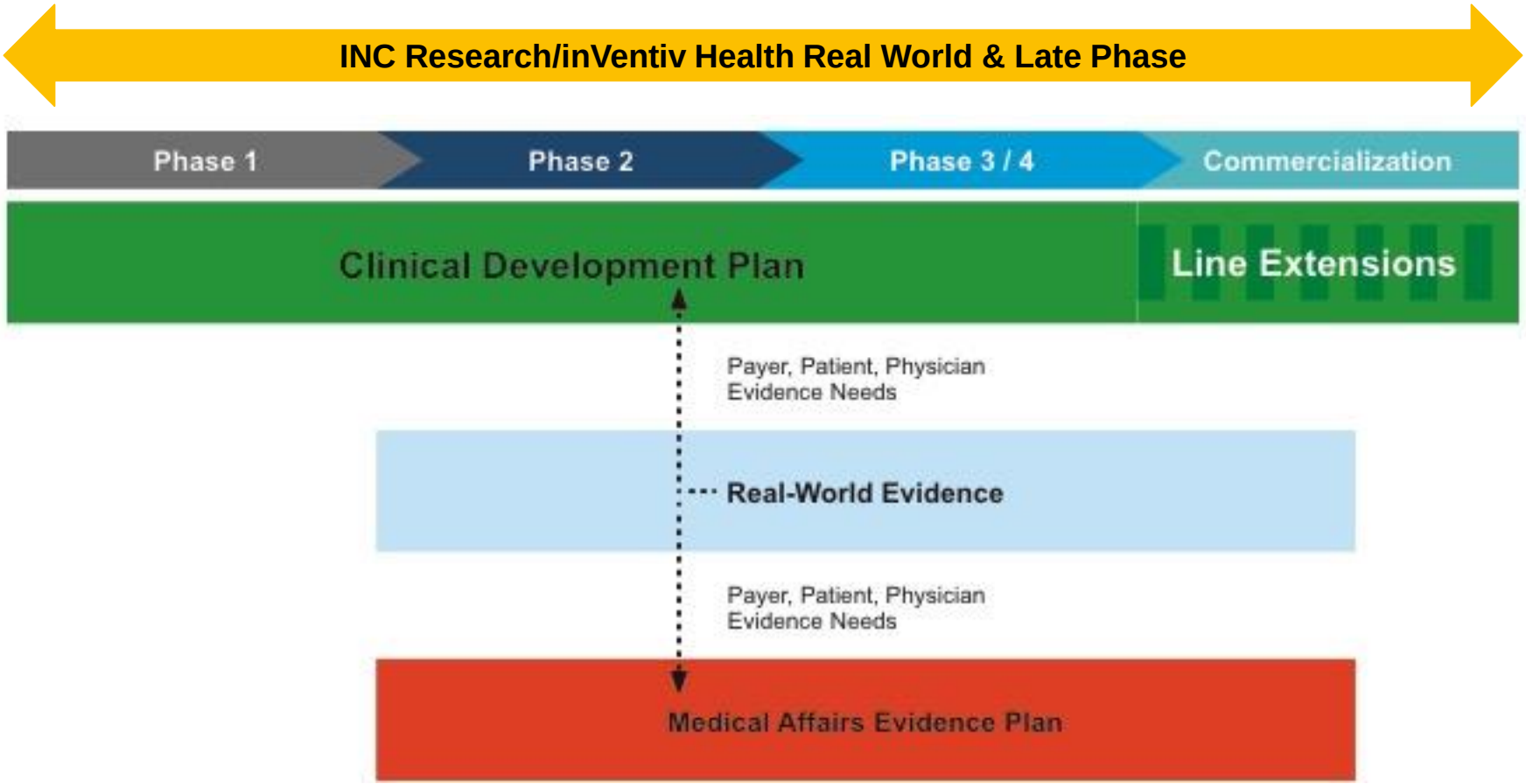
Source: EvaluatePharma; McKinsey analysis

An Integrated Medical Plan addresses obstacles to access ahead of time

- Current probability of a good drug launch = **1/3**
- **2/3** drug launches fall short of expectations

Create an Integrated Medical Plan

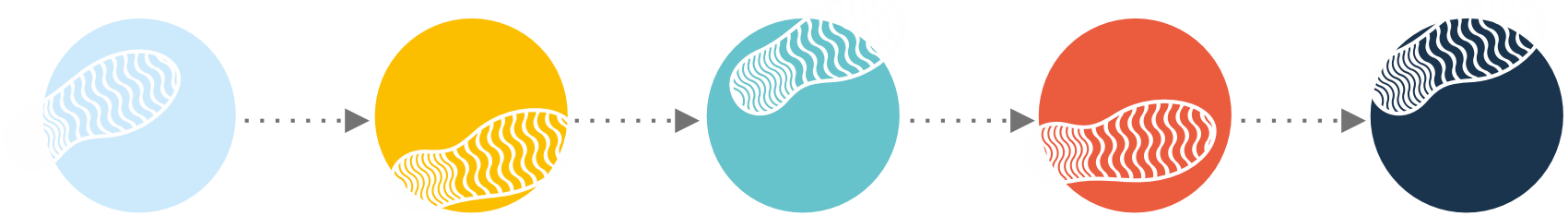
Begin with the end in mind



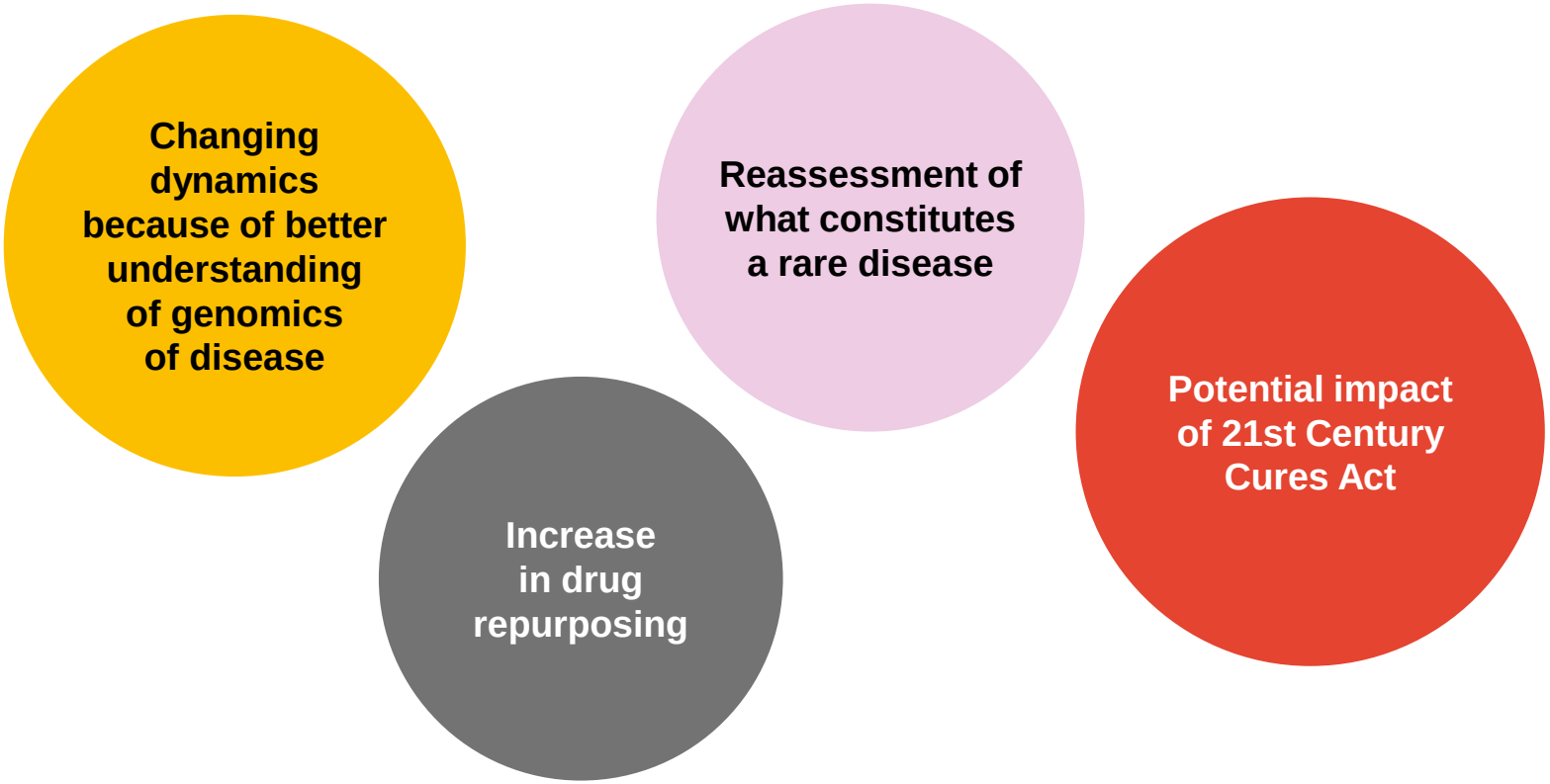
Current Trends and Challenges affecting Rare Disease

Challenges in Rare Disease Clinical Development

- Acceptability of placebo control design
- Identifying the patients who are likely to have a response to treatment – targeted patients approach
- Lack of previously recognized end points and poorly characterized, heterogeneous rates of disease progression
- Post-marketing requirements, including registries and their adaptation over time to reflect new information learned
- High risk and high potential clinical development area
- Price negotiation versus evidence collected



Current Trends



Current Trends

Changing dynamics because of better understanding of genomics of disease

•Rapid implementation of genomic technologies leading to the development of genetically targeted therapies to address these unmet medical needs

•The market has recently experienced an incredible simultaneous maturation of both discovery platforms, as well as targeting and delivery systems, including clinically effective gene therapy vectors, targeted and stabilized oligonucleotides, and RNAi technology

•*Nusinersen, a next generation modified RNA oligonucleotide technology, directly affects SMN protein production in patients with spinal muscular atrophy (SMA)*

Current Trends

Increase in drug repurposing

•It is a valid approach for rare diseases where there is a huge need for new treatments, but little funding available for conventional drug discovery

• Some recent examples:

Nicotinamide for Friedreich's Ataxia
Sildenafil use in Pulmonary Arterial Hypertension

Exenatide, a diabetes drug, is looking very promising in Parkinson's. Recent studies suggest problems with insulin signalling in the brain could be linked to neurodegenerative disorders,

Current Trends

Reassessment of what constitutes a rare disease

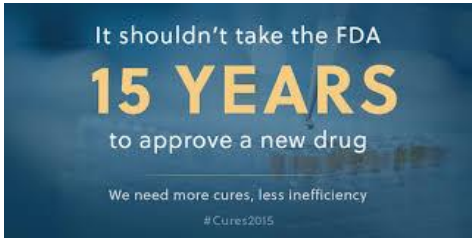
"Salami slicing" due to a better understanding of the genomics of disease

- For example, for decades colorectal cancer was considered to be a homogeneous entity and was treated as such. However, as colorectal cancer becomes better categorized by its molecular characteristics (e.g., *KRAS* negative–*BRAF* V600E positive), we may end up with many different types of colorectal cancer, some of which have been discovered and are now being treated according to their molecular status. This new understanding of colorectal cancer means that in the future each of these distinctive cancers could qualify as a rare disease. (*Evangelatos and Brand, NEJM, 2107;376*)

A series of articles in NEJM during April 2017

Current Trends

Potential impact of 21st Century Cures Act



The passing of the 21st Century Cures Act will drastically change the way drugs are approved by the Food and Drug Administration (FDA) and will allow for faster discovery, development, and delivery of treatments. This creates exciting new possibilities for increasing the number of novel therapeutics for rare diseases.

21st Century Cures Act

How will it help people with Rare Disease?

- Inclusion of the Rare Pediatric Disease Priority Review Voucher (PRV) program, which was set to expire. This provides incentives for pharmaceutical companies to develop drugs for rare pediatric diseases. The National Organization for Rare Disorders (NORD) projects that the extension of the PRV program will lead to the development of new therapies that will help more than 15 million children with rare diseases.
- Introduces a series of changes to the FDA drug approval process, including streamlining the review of genetically targeted therapies for rare diseases and offering an alternative to multiphase clinical trials (e.g. use "surrogate endpoints" rather than the traditional hard outcome to obtain approvals)
- Real World Evidence data that shows statistical association will now be considered during the approval process

Current Trends

Impact of 21st Century Cures Act

Innovation

- Clinical Data Use
- Adaptive Trials Designs
- Acceptance of biomarkers

For Pharma Industry

- Accelerate Orphan Drug developent
- Shorter timelines for Drugs from Bench to Bedside

Collaboration

- Patient communities
- Patient Advocacy Groups
- Interdisciplinary approach
- Cooperation between stakeholders

Overcoming some of these challenges with Real World Evidence

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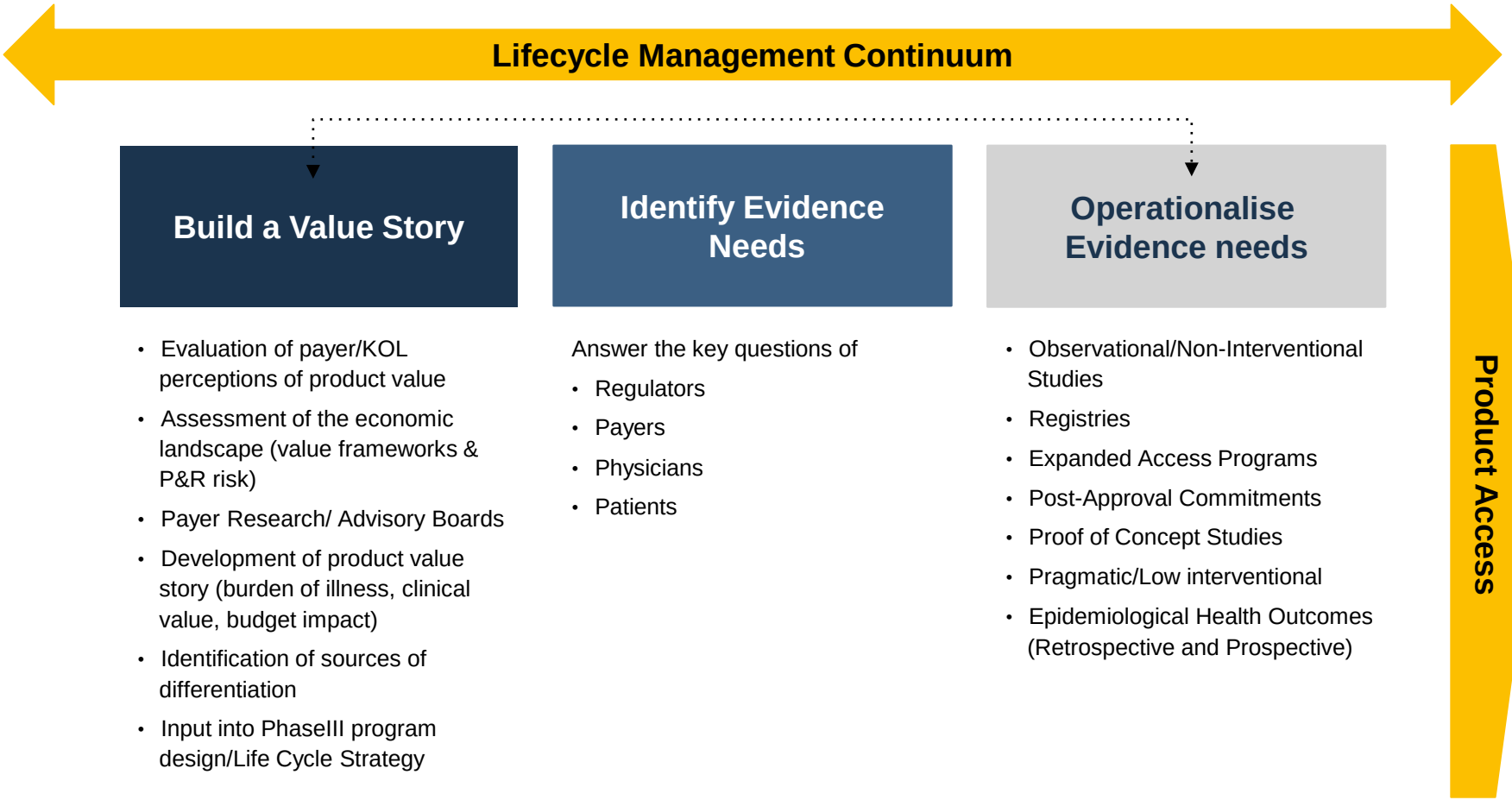
From concept through commercialization



7 key payer questions

7 key prescriber questions

7 key patient questions

Rare Disease Case Studies Demonstrating Value

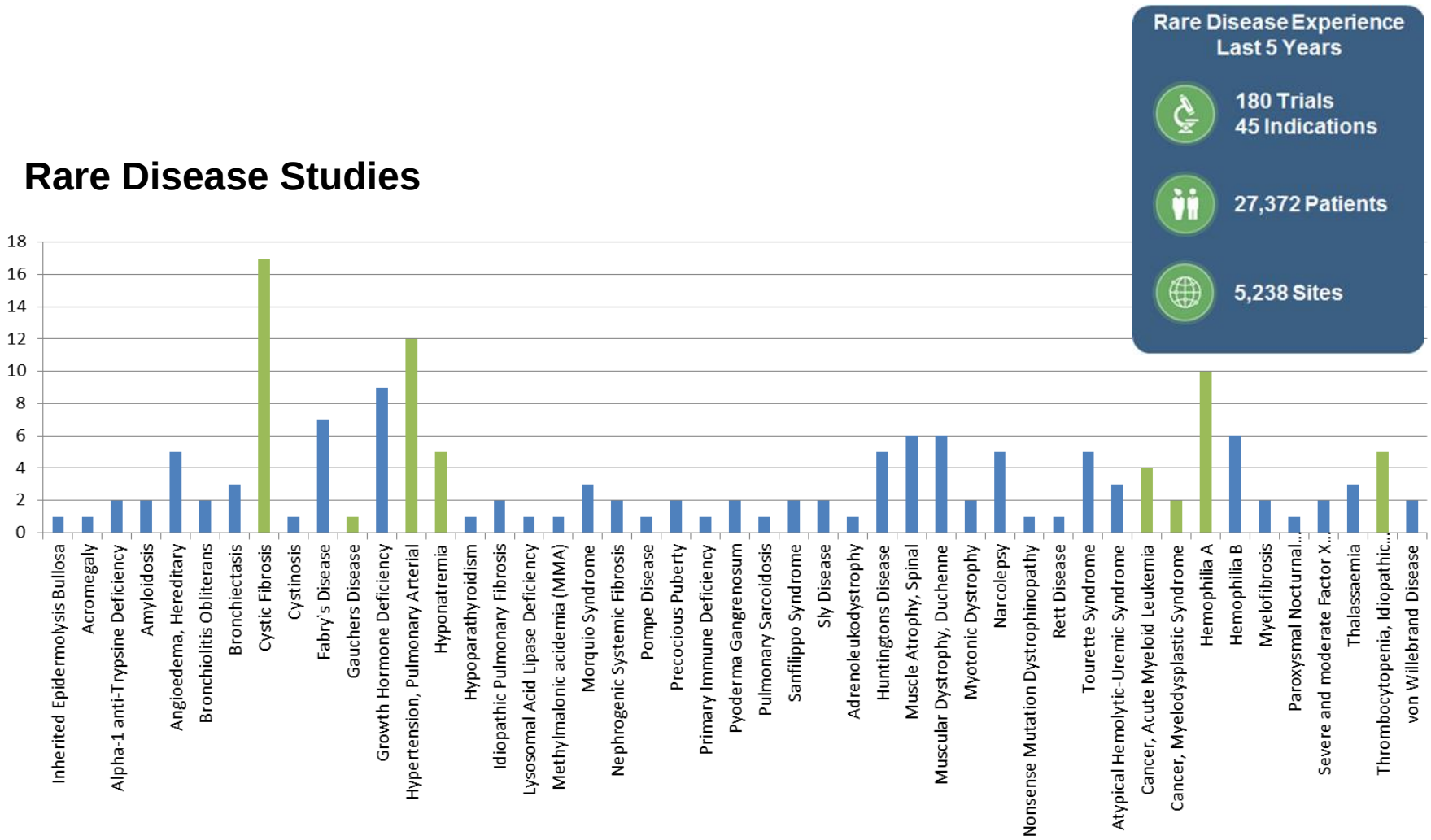
Study Type	Study Purpose	Value Demonstrated
Multi-Center, multi-national treatment extension for Pediatric and Adult Patients with Lysosomal Acid Lipase Deficiency	To demonstrate the safety and efficacy of drug. For treatment extension, commercial planning, and compassionate use upon regulatory approval	1. Additional agency approvals and minimal disruptions to medication between study and post-study treatments. 2. Minimal patient visit and treatment interruptions 3. Timely patient conversions,
Disease Registry with Pediatric and Adult Patients Case Study: Observational, non-interventional, prospective, multi-center, multi-national	Collect long term data to understand patient pathway	Building confidence in product in current indication and capture data on modifications
A Prospective Cross-Sectional and Longitudinal Study with Additional Retrospective Chart Review to Evaluate Clinical and Biochemical Characteristics and Disease Progression in Patients	Collect data for clinical characteristics and disease progression	1. Foundation for a rational drug development program 2. Will support the design of future clinical studies 3. Natural history data, to permit a detailed and systematic evaluation

Our Experience

Our Multi-Disciplinary Approach

Rare Disease experience

Rare Disease Studies



Dedicated Real World & Late Phase Business Unit

Maximizing value from Concept through Commercialization

>25 Years experience

In designing and conducting global RWLP studies (IIIb/IV) including expanded access programs, pragmatic clinical trials, patient and disease registries, PASS, PAES and epidemiological health economics and outcomes studies

Real world evidence

Partnering with our customers to Maximise Value by Providing Consultative and Operational Expertise in Real World Data Generation, from Concept to Commercialization

Global Expertise

- >380 Real World and Late Phase studies since 2012
- >500 staff supporting Real World & Late Phase studies globally

Fit For Purpose

- Technology
- SOPs and Work Instructions
- Data Platform
- Site Management and Remote Site Monitoring

Our Experience

Interventional	Non-Interventional	Scientific Advisory
Phase IIIb Clinical Trials	Post-Authorization Drug Safety & Effectiveness Studies (PASS/PAES)	Regulatory Compliance and Training (NIS, EAP, CUPs)
Phase IV Clinical Trials (including Interventional PASS)	Retrospective or Prospective Observational Studies (Registries)	Biometrics and Data Analytical Services
Pragmatic Clinical Trials	Multi-National Chart / EMR Reviews	RWE Scientific Advisory
Expanded Access and Compassionate Use	Epidemiology Studies	Preference Based Studies
	HEOR	
	Time & Motion Studies	

In Summary

- Due to the current Healthcare landscape, it is **never** too **early** to consider commercialization in drug development
- Despite efforts, the majority of drug launches **do not go as planned**
- There are some significant developments in the Rare Disease and Orphan Drug area, particularly in the Regulatory environment, where the value of Real World Evidence will be high
- An **Integrated Medical Plan (IMP)** is an essential tool to ensure that the different needs of the stakeholders involved (Regulators, Payers, Physicians and Patients) are addressed appropriately
- Having an IMP significantly **increases your chances of drug launch success**
- INC Research has both the capabilities and experience to effectively deliver your real world evidence needs in rare disease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