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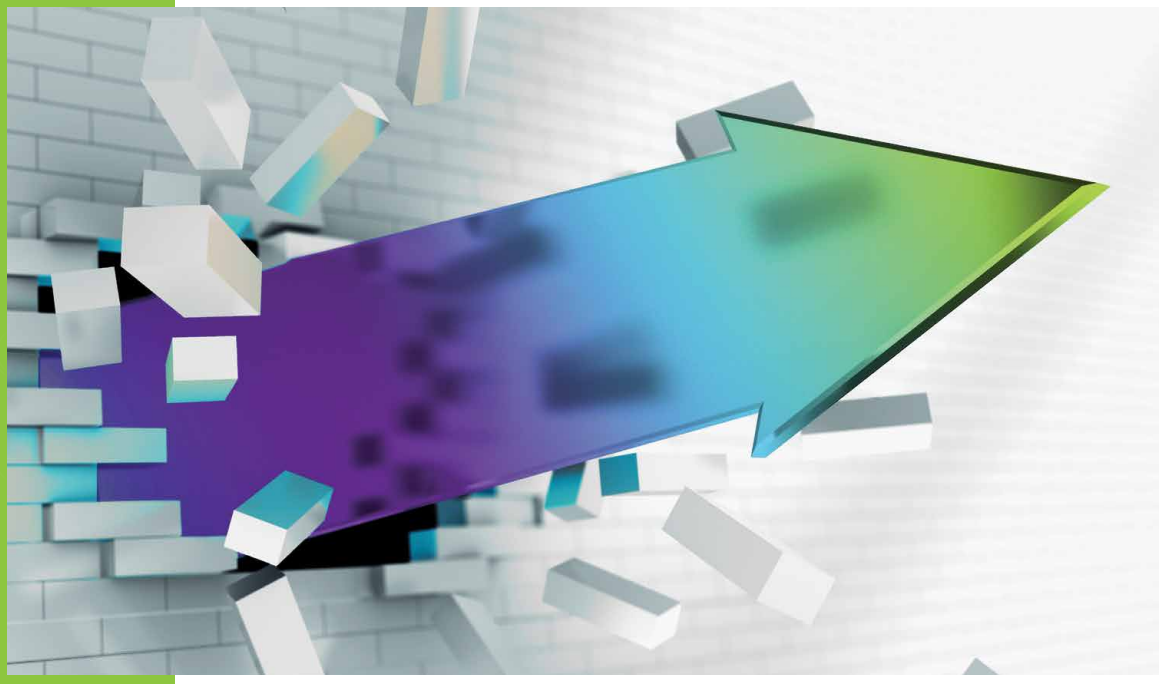

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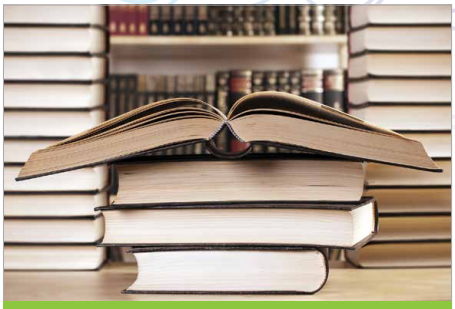

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Executive Director, Peri- and Post-Approval Interventional Studies
Evidera, a PPD business

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Executive Director, Integrated Solutions, Real-World Evidence
Evidera, a PPD business

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Vice President, Epidemiology and Head of Strategic & Scientific Affairs, Real-World Evidence
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Rare Disease and Orphan Drug Development Overview

Although there is no singular definition of rare diseases, the term is typically applied to diseases or subsets of common diseases affecting fewer than 200,000 people in the United States (US)[1]; fewer than five per 10,000 in the European Union (EU)[2]; and fewer than 50,000 patients in Japan.[3] There are approximately 7,000 rare diseases, which collectively affect approximately 400 million people

globally,[4] many of whom suffer from high disease burden and limited treatment options. When we also consider caregiver burden, the impact of rare diseases impacts even more people. These rare pathologies, many of which are serious or life-threatening, include genetic defects, autoimmune disorders, infectious diseases, neurological disorders, and certain types of cancers,[5] among others.

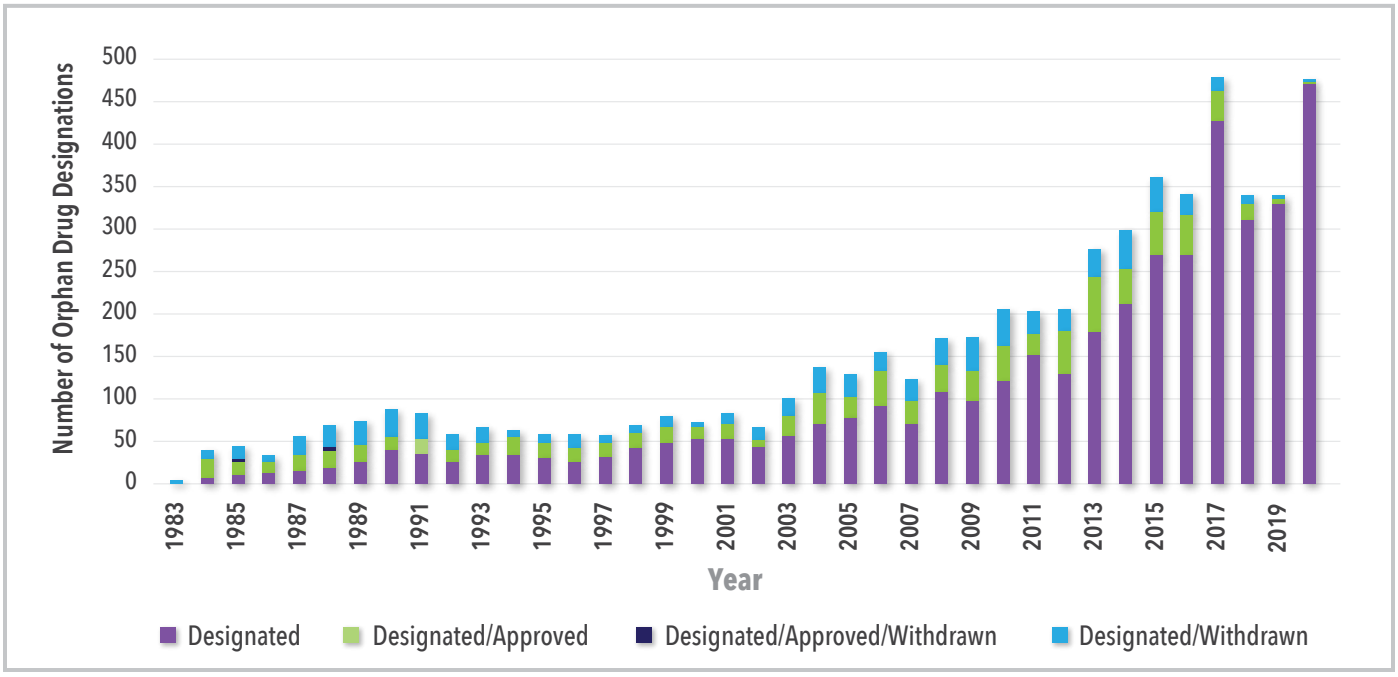
Since the enactment of the US Orphan Drug Act in 1983,[6] the EU Regulation 141/2000 on orphan medicines in 2000,[7] and, most recently, the US 21st Century Cures Act in 2016,[8] many advancements have been made in the development of treatments for rare diseases. The drive for international collaboration on rare diseases has been further supported by laws such as the US Rare Diseases Act in 2002,[9] which established the Rare Diseases Clinical Research Network (RDCRN) as an initiative of the Office of Rare Diseases Research (ORDR) at the National Institutes of Health's (NIH's) National Center for Advancing Translational Sciences (NCATS). The RDCRN comprises 23 research consortia and pioneered the creation of a collaborative and coordinated network of investigators and patient groups to support research into rare diseases.[10] More recently, other rare disease organizations have encouraged the involvement of patients in the design of clinical studies in rare diseases. For example, the goal of the European Organisation for Rare Diseases (EURORDIS), which has published a charter for the collaboration between study sponsors and patient organizations, is to improve the quality of clinical research in rare diseases[11] by statutes such as Directive 2011/24/EU.[12] This has resulted in the establishment of European reference networks between healthcare providers and centers of expertise in the EU member states, increasing access to cross-border healthcare and opportunities for patients to participate in research by facilitating cross-border enrollment.

Since the introduction of the Orphan Drug Act, more than 5,700 drugs and biologics have been given orphan drug designation by the US Food and Drug Administration (FDA). However, data from the FDA Orphan Drug Database (see *Figure 1*), demonstrate that the conversion rate to approval is low, with only 935 candidates (16.3% of all initially granted orphan drug designation) ultimately approved for use and almost the same number withdrawn (803 [14.0%]). Furthermore, this trend has not improved over the last decade. Similarly, an analysis of data from the EU demonstrated that 27.8% of all orphan drug designations granted in the period from 2000 to 2012 failed.[13] Consequently, only 5% of rare diseases currently have an approved medicinal therapy.[4] However, it is noteworthy that the number of US orphan drug designations granted over the last two years remains high, indicating continued strong interest in pursuing treatments for rare diseases, even in the midst of the COVID-19 pandemic.

Impact of COVID-19 on Rare Disease Patients

Patients with rare diseases have been widely impacted by the COVID-19 pandemic as evidenced by EURORDIS and the US National Organization of Rare Diseases (NORD) surveys, in which 90% and 74% respectively[15,16] of these patients experienced interruptions in their continuity of care. The ability to access clinical research has also been impacted by the pandemic.[17] Data obtained by the authors from ClinicalTrials.gov (see *Figure 2*) show a greater than 500% increase in the number of studies suspended in 2020 (vs. 2019). Furthermore, a recent report by McKinsey,[18] which surveyed 20 European and US cell and gene therapy

Figure 1. Distribution of FDA Orphan Drug Designations by Year[14]



companies, revealed that the COVID-19 pandemic has had a major impact on clinical development, with 65% of respondents reporting average delays to programs between 3-12 months, and 55% reporting paused site activations and enrollment and missed follow-up visits. Preliminary findings from the RDCRN's COVID-19 impact survey indicate that approximately 40% of patients were unable to continue specialized treatments for their disease during the pandemic.[19]

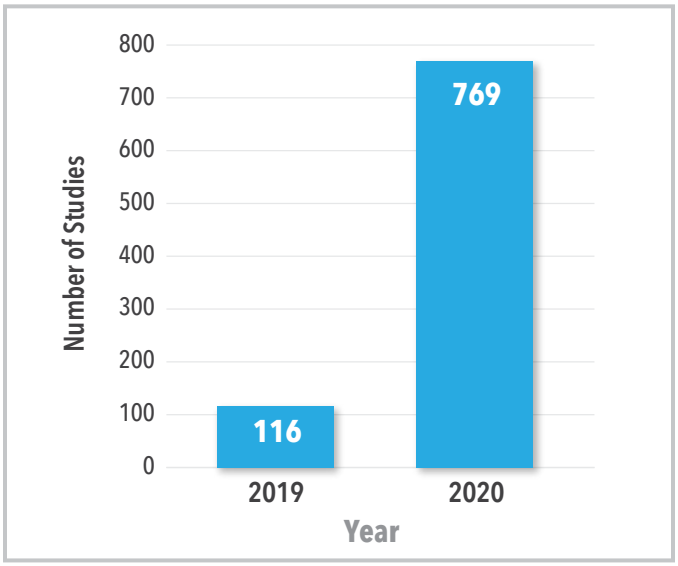
This paper examines the traditional challenges of drug development in rare diseases coupled with the once in a lifetime challenge of the COVID-19 pandemic, which has forced changes in nearly all spheres of life, including how we communicate, how we work, how healthcare is delivered, and how we conduct clinical research. Although COVID-19 has compounded many of the challenges of conducting research in rare diseases, it has paradoxically also led to advancements that have enabled research to continue and evolve. As we now begin to emerge from the pandemic, our challenge is to ensure we build back better and for the benefit of rare disease patients and their families.

Challenges of Conducting Rare Diseases Research

Rare disease research and orphan drug development is challenging in the best of times, and the financial rewards for companies that develop treatments for rare disease populations can be low considering the R&D investment required versus the size of the affected population. Some of the main challenges to confront when conducting rare disease research are summarized in *Figure 3* and discussed below.

Enrollment of patients with rare diseases in clinical studies is challenging, and a recent analysis of studies terminated early found lack of patient accrual to be the main reason for study failure.[20] Populations with rare diseases are, by their nature, small and typically geographically dispersed[21] and are, therefore, challenging to include in sufficient numbers required for clinical studies. Further complicating this enrollment challenge is the lack of solid epidemiology on many rare diseases, including: (1) limited awareness of relevant signs and symptoms by healthcare professionals; and (2) heterogeneity of clinical presentations that can make a diagnosis via the appearance of clinical signs and symptoms alone difficult, necessitating genetic testing and genetic counseling. These complications often result in underdiagnosis or misdiagnosis, for example Fabry disease, where it is thought that only approximately 20% of cases in the US have been diagnosed.[22] Heterogeneity of clinical

Figure 2. A Comparison of Suspended Clinical Studies 2019 to 2020



Source: Clinicaltrials.gov

Figure 3. Challenges of Conducting Clinical Research in Rare Disease

presentations can also make it difficult to identify suitable cohorts of sufficient size for inclusion into clinical studies (including matching controls if using external control arms).

Approximately 50% of patients with rare diseases are children, which presents additional challenges in terms of:

- **Dose selection** – appropriate pediatric dose selection is required to maximize the likelihood that the studied dose will have a beneficial efficacy and safety profile in children
- **Endpoints and outcomes selection** – endpoints and outcome measures of interest in children may differ from those typically used for adults
- **Blood sampling and tissue collection** – pharmacokinetic/pharmacodynamic (PK/PD) investigations can be difficult in neonates and infants due to limited blood volume; invasive procedures such as tissue biopsies and cerebrospinal fluid (CSF) sampling may not be justifiable in younger age groups
- **Adverse event reporting** – eliciting adverse event information can be challenging in children in whom vocabulary is limited and/or non-verbal communication with caregivers more common
- **Informed consent** – the complex nature of assent; the impact of cultural variables and individual life experiences leading to reluctance on the part of parents and caregivers to expose dependents to experimental treatments; and gaps in local regulations all present challenges
- **Logistics and visit scheduling** – participation may be hindered by mobility difficulties, school and family schedules, the need to travel long distances, and potential loss of income for parents due to the need to take time off work

Randomized clinical trials (RCTs), although the gold standard for evidence generation, are often not possible in rare disease research due to lack of comparator treatment options and ethical concerns with the use of placebo-controls, which, even if possible, may be difficult to sustain for long-term comparisons. Thus, it is not uncommon for studies in rare diseases to be single-arm trials focused on enrollment of patients from a limited number of specialized centers in countries with relatively high prevalence of the disease. This traditional approach seems to be an intuitive solution shaped by practical necessities and limitations, such as small patient populations, limited comparator options, and high unmet medical need, which can make a two-arm study impractical and/or unethical. However, this traditional study approach creates a barrier to access of novel and potentially life changing therapies for patients who live outside the catchment of a specialist treatment center or who are living with a high disease burden and medical needs that make travel difficult. In addition, the traditional model limits the conclusions that can be drawn from the research. External control arms (ECAs) are one possible solution to facilitate interpretation of single-arm studies. However, the heterogeneity of clinical presentations that can make the diagnosis of rare diseases challenging also poses challenges for ensuring comparability of cohorts when designing an ECA.

Heterogeneity of clinical presentations of rare diseases also poses challenges for endpoint selection. Different mutations producing gene variants that result in different clinical manifestations of a disease, such as those seen in Fabry disease, can affect multiple organ systems to varying degrees and researchers must therefore consider which is most important, which is most likely to respond to therapy, and how to measure response with accuracy and precision. In addition, the type of treatment can present challenges for identifying the most appropriate endpoint or outcome, for example, long term treatment outcomes in advanced therapy medicinal products (ATMPs) such as gene and cell therapies. This underscores the importance of natural history studies to better understand disease progression and burden of disease.

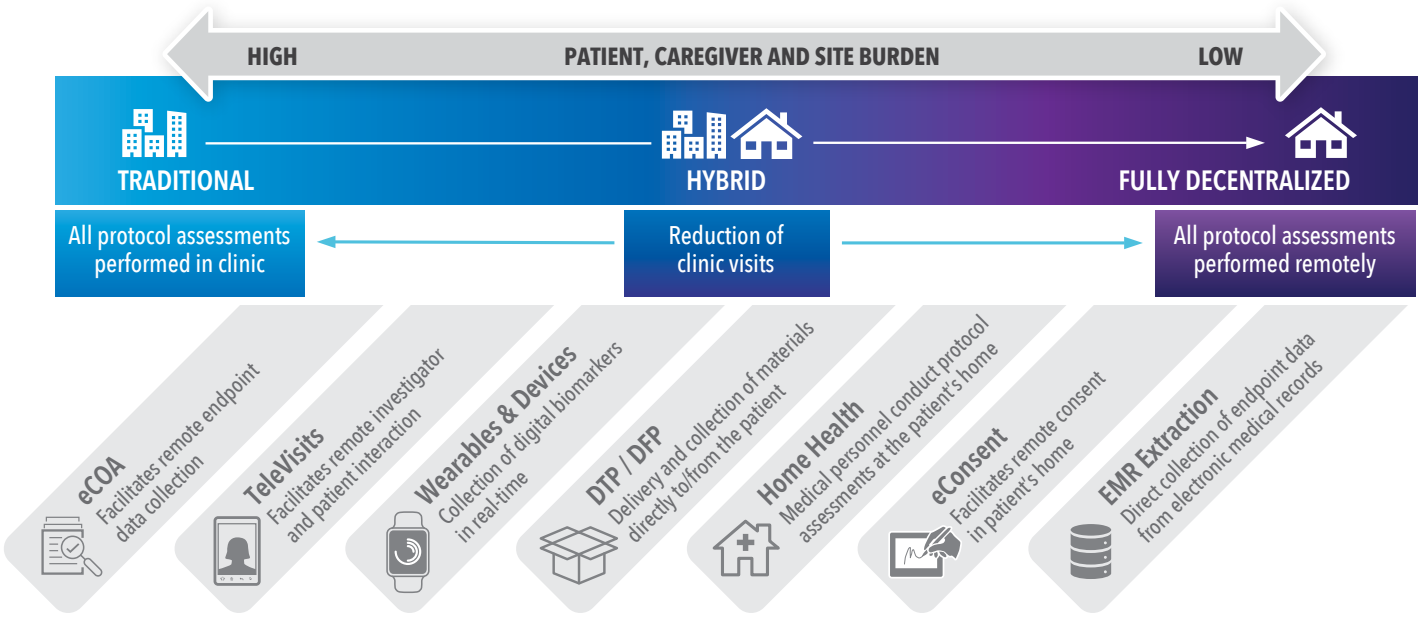
Several key challenges of rare disease research have been compounded by the COVID-19 pandemic, including the ability or willingness of patients and their families to travel, and reduced access to specialist medical care and testing facilities, resulting in potential additional delays in diagnosis and treatment. Risk of COVID-19 infection and its potential sequelae added to existing and significant medical challenges is another barrier. FDA guidance on conducting studies in the COVID-19 era emphasizes patient safety and sets forth the expectation that sponsors, investigators, and institutional review boards (IRBs)/independent ethics committees (IECs), respectively, put robust measures in place to maintain the safety of study participants and data integrity. While challenging in general, it is particularly keenly felt in the setting of rare diseases, where stakes are high and suspension of a study or no access to study medication outside of a study can be devastating and even life threatening. The greater than five-fold increase in the number of trials suspended in 2020 (vs. 2019) (see *Figure 2*) demonstrates that these concerns are not hypothetical or academic, but rather have already conspired to delay the evaluation of potentially life-changing therapies.

Addressing Barriers to Rare Disease Research

Decentralized Study Approaches to Remove Geographical Barriers

As previously mentioned, the reality of disparate geographic distributions of patients with rare diseases often results in patients needing to travel long distances to access specialist treatment and studies. These realities, which challenge the traditional site-based clinical study model, have only been compounded by the COVID-19 pandemic. Simultaneously, COVID-19 has accelerated a paradigm

Figure 4. The Spectrum of Study Solutions From Traditional to Fully Decentralized



eCOA = electronic clinical outcomes assessment; DTP/DFP = direct to patient/direct from patient; EMR = electronic medical records

shift towards digital enablement and decentralization of studies, which have enabled the continuation of clinical development programs. Removing geographical barriers by bringing studies to patients is a compelling solution that increases patient access to clinical research and may, if supported by carefully considered decentralized solutions, improve completeness of the data collected. There is no one-size-fits-all solution to clinical studies and certainly not studies in patients with a rare disease. These solutions exist along a continuum, from traditional site-based models that are supported by digital health tools, to fully decentralized studies (DCTs) where a full range of remote enablement solutions are deployed. *Figure 4* illustrates the menu of DCT solutions that can be employed to support the full spectrum of studies.

A recent study by the Tufts Center for the Study of Drug Development (Tufts CSDD), which interviewed staff from 25 US-based pharmaceutical, biotechnology, and non-profit research institutions, found that telemedicine and eConsent were the most frequently mentioned remote technologies adopted during COVID-19; and telemedicine was implemented by 19 of the interviewed organizations.[23] Home health, direct to patient (DTP) supply, and decentralized labs were the most utilized strategies in studies of rare diseases. Despite the ability of these DCTs to reduce delays in clinical research, some have predicted that studies will return to the traditional approach post-COVID-19—especially for rare diseases and oncology, where many stakeholders believe that in-person care is critical. However, a recent survey by the rare disease patient network, Raremark, found that rare disease patients are open to a decentralized approach,[24] suggesting that in-person care may not be such a key consideration for patients.

The ability to collect digital biomarkers via wearables has the potential to expand the possibilities for conducting DCT studies in rare diseases. A wearable that enables continuous monitoring of physical activity has been piloted in patients with Gaucher disease,[25] a rare lysosomal storage disorder. This disorder is categorized into three subtypes: Type 1 which is associated with pathology of the liver, spleen, and bone tissue, but does not affect the central nervous system (CNS); and Types 2 and 3, which do affect the CNS, resulting in neuromuscular impairment as well as non-neurological disease. The study, which monitored physical activity via a 3D accelerometer worn on the wrist paired to a mobile phone app that enabled patients to complete self-reported outcome measures, demonstrated the feasibility and utility of this technology to monitor physical activity as a surrogate of disease activity in a real-world setting. If further validated, this could expand the possibilities of performing DCTs in this patient population and potentially add to the list of more traditional surrogate endpoints already approved by the FDA for rare disease indications that lend themselves to remote collection (*Table 1*).

Mining Electronic Medical Records (EMRs) to Accelerate Rare Disease Diagnosis and Narrow the Search for Rare Disease Populations

The increasing availability of rich EMR data that are potentially linkable to medical claims data, and our ability to mine those data using natural language processing (NLP),

Table 1. Surrogate Endpoints Used as the Basis for FDA Approval in Rare Disease Indications That Can Be Collected Remotely

Disease or Use	Surrogate Endpoint	Type of Approval Appropriate	Drug Mechanism of Action	Age Range
Acromegaly	Serum Insulin-like growth factor-I (IGF-1)	Traditional	Growth hormone receptor antagonist	2 years to less than 18 years
Sickle cell disease	Hemoglobin response rate	Accelerated	Hemoglobin S polymerization inhibitor	12 years and older
Cystic fibrosis	Forced expiratory volume in 1 second (FEV1)	Traditional	Cystic fibrosis transmembrane conductance regulator potentiator	2 years and older
Cystinuria	Urinary/urine cystine	Traditional	Reducing and complexing thiol	9 years and older
Homozygous sitosterolemia (phytosterolemia)	Plasma sitosterol and campesterol	Traditional	Dietary cholesterol absorption inhibitor	No age range specified
Hypercholesterolemia	Serum LDL-C	Traditional	Lipid-lowering	No age range specified
Hypothyroidism	Thyroid-stimulating hormone (TSH)	Traditional	Thyroid hormone analog	No age range specified
Lipodystrophy	Serum hemoglobin A1C, fasting glucose and triglycerides	Traditional	Leptin analog	No age range specified
Lysosomal Acid Lipase (LAL) deficiency	Serum LDL-c levels	Traditional	Hydrolytic lysosomal cholesteryl ester and triacylglycerol-specific enzyme	Birth to less than 18 years of age
N-acetylglutamate Synthase (NAGS) deficiency	Plasma ammonia	Traditional	Carbamoyl Phosphate Synthetase 1 activator	From birth to less than 18 years of age
Phenylketonuria	Plasma phenylalanine	Traditional	Phenylalanine hydroxylase activator	1 month to less than 18 years of age
Primary hyperoxaluria type 1 (PH1)	Urinary oxalate	Traditional	siRNA against hyroxyacid oxidase 1 gene	No age range specified
X-linked hypophosphatemia	Serum phosphate	Traditional	Fibroblast growth factor 23 inhibitor	1 year and older

Source: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

artificial intelligence (AI), and other advanced analytic methods, have expanded the possibilities of identifying:

1. Patients with rare diseases through computable clinical phenotypes (i.e., observable and searchable physical, morphologic, or biochemical characteristics), [26,27] and
2. Those not yet diagnosed whose clinical profiles suggest confirmatory testing may be warranted (providing at least in theory the opportunity for improved case finding, with benefits to affected individuals that include and exceed enrollment in clinical studies).

Several resources exist that can aid in the development of probabilistic search algorithms that can be applied to EMR for the purposes of identifying rare disease populations. For example, the Orphanet Rare Disease Ontology (ORDO), jointly developed by Orphanet and the European Bioinformatics Institute (EMBL-EBI), is a structured vocabulary for rare diseases that provides a useful resource for computational analysis.[28] The encyclopedia of Rare disease Annotation for Precision Medicine (eRAM) provides computational annotations (a process that attributes a biological function to genes) for approximately 16,000 rare diseases, producing more than 6,000 human disease related phenotype terms.[29] Furthermore, the Human Phenotype Ontology (HPO), developed from medical literature and various rare disease resources, provides standardized vocabulary of phenotypic abnormalities encountered in human disease.[30] These resources are being used to generate algorithms to extract phenotype-disease associations to support rare disease differential diagnosis.[31] One such innovative tool is Dx29, which is being developed by Foundation 29, a non-profit organization focused on applying the latest AI technology to support rare disease diagnosis as well as building the rare disease knowledge base.[32] Dx29 is part of a key technology pilot program supported by The Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease[33] that combines the HPO with natural language processing and next generation sequencing technology to extract rare disease phenotypes from free text medical records to narrow down possibilities for diagnosis.[34]

While promising, challenges exist in implementing data mining approaches to rare diseases research in multi-center/multi-country studies. For example, applying coding algorithms across diverse EMRs likely require the enablement of different software systems and associated data formats to interact with others (i.e., interoperability). Common data models (CDMs), such as the one that is part of the FDA's Sentinel System, have been used to standardize EMR data across multiple sources for research purposes. However, CDMs have traditionally relied on the extraction and mapping of structured data such as ICD-9-CM diagnosis and procedure codes. These alone may not translate to a broad clinical research setting or be sufficient to identify potential participants in rare diseases studies, because clues to the diagnosis may be buried in the unstructured portions of patient records, such as physician notes or discharge summaries (which often contain misspellings, abbreviations, and local colloquialisms that require substantial cleaning and review before they can be fully analyzed/incorporated into case-finding algorithms). The mapping of data can also result in loss of detail and precision, further limiting the usefulness of this approach in rare disease research. However, recently HL7's Fast Healthcare Interoperability Resources (FHIR) has emerged as a new data standard and Application Programming Interface (API) that is able to integrate both structured and unstructured EMR data. FHIR has recently been used with semi-structured discharge summaries to identify patients with obesity and its multiple associated comorbidities and could be similarly used to narrow the search for patients with (at least some) rare diseases. However, heterogeneity of clinical presentation in patients with a rare disease can make identification through these automated means alone difficult (in the aforementioned Gaucher disease example alone, there are three different clinical manifestations that each have different hallmark symptomatology). Therefore, confirmation of diagnosis via genetic testing is often needed, although use of the EMR and advanced analytics such as machine learning can likely maximize efficiencies in identification of the pool of patients requiring this confirmatory step.

The use of EMR extraction to obtain endpoint data can also streamline data collection and reduce site burden. However, this can be challenging in patients with rare diseases for whom specialist examinations and test results may be buried in the unstructured data portions of ERMs or locked in paper records; information from visits with specialists outside the patient's typical network of providers may not be entered completely into the EMR, further limiting their usefulness. The use of specialized EMR software (e.g., ophthalmology-specific systems such as Softalmo [Corilus]), that contains specific fields for capturing specialist information and examination results, has been demonstrated to improve the reliability of EMR data in patients with rare eye disorders, and may facilitate the collection of endpoint data via EMR extraction.[35] This technology may also facilitate the design and conduct of pragmatic clinical studies, as it would allow for a more "hands off" approach without a corresponding threat to the capture of necessary endpoint data.

Genetic Screening to Identify Patients with Mutations of Interest

Approximately 80% of rare diseases have a genetic component, and advances in technology, such as next generation sequencing (NGS), have led to the identification of new molecular biomarkers. These are integral to the development of novel treatments and have the potential to identify subgroups of patients suffering from, or at risk of, more common diseases (e.g., genetic mutations linked to obesity). This has led to progress in rare disease drug

development that previously had been difficult to treat (e.g., PARP inhibitor olaparib approved for the treatment of a rare and lethal form of breast cancer[36]). Many patients with rare diseases may already be participants in clinical studies; consequently, genetic screening to identify newly diagnosed, treatment-naive cases may be warranted. Genetic testing of potential patients for rare disease mutations identified through case-selection algorithms developed through EMR mining and machine learning is one approach. Another important strategy, although not new to rare disease research, is cascade testing of family members of patients diagnosed with a rare disease. *Figure 5* shows a schematic for a virtual genetic screening program that the authors have successfully deployed in rare disease clinical programs. This strategy is now being supported by companies like PreventionGenetics, an accredited clinical DNA testing laboratory (Marshfield, Wisconsin, USA), which has partnered with several biopharmaceutical companies developing treatments for rare disorders to offer no-cost sponsored testing programs.[37]

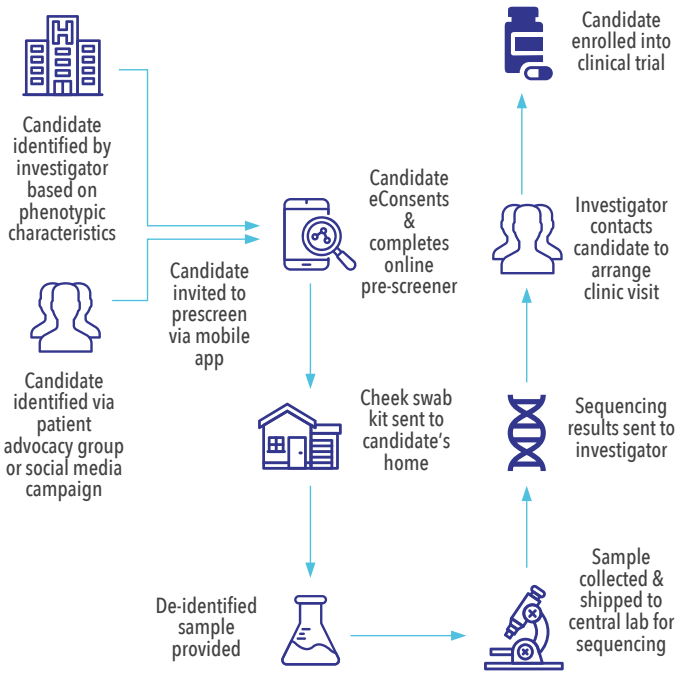
Use of Natural History Studies and Registries to Characterize Rare Disease Patient Populations and Serve as ECAs

The FDA's updated draft guidance on rare diseases[38] includes a recommendation to conduct natural history (NH) studies to better characterize patient populations and delineate target populations. Further FDA draft guidance in 2019[39] underscores the importance of performing NH studies to expand on the paucity of data for many rare diseases; this expanded knowledge base can then be used to support and guide the design of clinical studies. NH studies can inform clinical product development by:

- Providing better insight into disease characteristics, patient populations, and identification of disease subtypes
- Identifying patients for clinical studies
- Serving as an historical external comparator in case of single-arm studies, thereby addressing some limitations inherent in single-arm studies, ethical concerns with use of placebo or sham comparators, and reducing the number of patients that need to be enrolled[40]
- Identifying the most sensitive and relevant endpoints or the optimal duration of follow-up
- Providing the ability to characterize disease burden and levels of unmet need associated with current standard of care, thereby demonstrating the need for new therapies in the indication and potentially providing input values for economic models typically required for newly approved products

Global rare disease patient registries created through collaboration between multinational rare disease

Figure 5. Identifying Patients for Rare Disease Studies Through Genetic Screening



organizations such as NORD, EURORDIS, and the Canadian Organization for Rare Disorders (CORD) are powerful web-based data repositories containing treatment-related health information and biological sample data. Furthermore, their corresponding biobanks, with a Global Unique Identifier (GUID), enable the tracking of patient information. These registries are excellent potential sources of data that could serve as historical ECAs in the case of single-arm studies and help identify appropriate endpoints, thereby reducing the number of patients that need to be enrolled and yielding potentially more comprehensive results. However, certain data elements are recommended for rare disease registries in order to inform clinical study design, including patient characteristics, demographic characteristics, specific diagnosis (e.g., for genotype/phenotype classification or other factors that may affect outcomes), comorbidities, treatments, mortality, life impact, and pathophysiological manifestations.[41] This level of detail is more likely to be captured in disease and treatment registries, but not captured in public health registries, which are focused on helping to inform epidemiological research, healthcare service planning, and disease surveillance.

If natural history studies or registry data are intended to serve as ECAs, it is recommended to seek preliminary regulatory agency agreement for the use of such designs ahead of submitting final protocols. ECAs have been successfully employed in several indications, and examples of FDA approvals based on clinical studies that incorporated ECAs include:[42]

- Blincyto (blinatumomab) for the treatment of relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia: historical controls were used to demonstrate effectiveness (vs. standard of care), based on weighted analysis of patient-level data from medical chart review
- Bavencio (avelumab) for the treatment of metastatic Merkel cell carcinoma and urothelial carcinoma: historical controls identified via EMRs and a German patient registry were used as a benchmark to characterize the natural history of the disease

Conclusion

The COVID-19 pandemic has widely impacted clinical research opportunities for patients with rare disease indications, many of whom fall into highly vulnerable categories with high disease burden and limited treatment options. This impact has been compounded by disparate geographic distributions of rare disease populations, often requiring patients to travel long distances to access specialized treatment, further exposing the limitations of traditional, site-based, clinical study models to recruit and retain enough patients to generate statistically meaningful results. Natural history studies and rare disease registries can serve as sources of external comparators, reducing the number of patients needing to be enrolled and yielding potentially more meaningful results. Leveraging technology can facilitate the research required to bring these life-changing medications to market, including but not limited to, identification of rare disease populations via computable clinical phenotypes using AI algorithms to mine EMRs, remote genetic screening, DCT solutions to bring clinical research into patients' homes, and the use of wearable technologies and EMRs to collect necessary endpoints. The use and acceptance of these technologies has largely evolved during the COVID-19 pandemic out of necessity. However, as we emerge from the pandemic, it is incumbent on us all to remember the lessons we have learned and continue to innovate and lead in the design and conduct of rare disease studies. These patients, and the caregivers who support them, deserve nothing but our best. ■

For more information, please contact info@evidera.com.

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The Evolution of Pregnancy and Lactation Safety Studies in the US and Trends in FDA Post-Marketing Requirements/Commitments

Kristin Veley, PharmD, MPH
Senior Research Scientist and Director of REMS and Pregnancy Registries, Real-World Evidence
Evidera, a PPD business

Deborah Covington, DrPH, FISPE
Senior Research Leader, Real-World Evidence
Evidera, a PPD business

Payal Pozin, MPH
Research Associate III, Real-World Evidence
Evidera, a PPD business

Kat Downes, PhD, MPH
Research Scientist, Real-World Evidence
Evidera, a PPD business

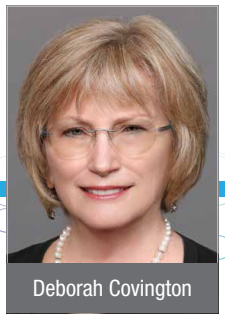
Rebecca Morris Buus, PhD
Senior Research Associate, Real-World Evidence
Evidera, a PPD business

Lindsey Wilson, BS
PPAS Data Collection, Real-World Evidence
Evidera, a PPD business

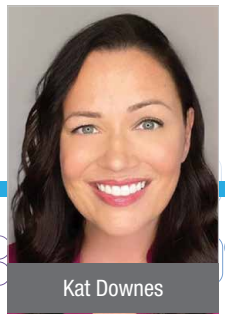
Introduction

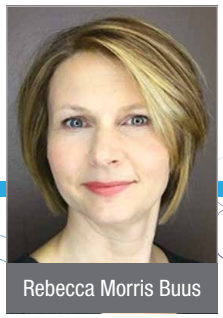
There is increasing interest in monitoring the safety of medication use during pregnancy and lactation. Studies to evaluate medication safety during pregnancy and lactation, as well as the regulatory initiatives in the United States (US) related to these studies have evolved over the past few decades.


Kristin Veley


Deborah Covington


Payal Pozin


Kat Downes


Rebecca Morris Buus


Lindsey Wilson

This paper examines:

- The history of pregnancy studies in the US
- The regulatory initiatives regarding pregnancy and lactation safety studies in the US
- The types of pregnancy and lactation safety studies currently required or recommended by the US Food and Drug Administration (FDA)
- Recent trends in post-marketing requirements (PMRs) and post-marketing commitments (PMCs) issued by the FDA for pregnancy and lactation safety studies and the potential impact of recent regulatory initiatives and guidance documents on these trends

Historical Perspective of Pregnancy Studies in the US

One of the first pregnancy safety studies conducted in the US was implemented by Burroughs Wellcome (now GlaxoSmithKline) in the mid-1980s. The company had just launched acyclovir, used to treat genital herpes. Because acyclovir was likely to be used by patients of childbearing potential and because earlier antiviral drugs tended to be toxic, the company decided to implement a pregnancy monitoring program with an active data collection system. Thus, one of the first pregnancy registries was voluntarily launched.[1]

The study was called a registry because the originators referred to it as an observational, case-registration follow-up study.[2] However, the study differed from other registries. The typical registry at that time was broad in scope and collected a vast amount of data over a long period of time. Such registries were used for multiple research studies. In contrast, the design of this pregnancy registry was targeted in scope. Healthcare providers voluntarily enrolled pregnant patients exposed to acyclovir during pregnancy and provided minimal data at enrollment and at pregnancy outcome. The primary focus was major congenital malformations (MCMs) and the observed risk of MCMs was compared with that of an external comparator, the Metropolitan Atlanta Congenital Defects Program.[3] While the registry sought to prospectively enroll and collect data on participants, retrospective data were also collected for signal detection purposes.

While methodologically flawed by today's standards, this early pregnancy registry provided valuable information to clinicians and their patients for weighing the potential risks and benefits of acyclovir treatment in patients of childbearing potential. It provided the company with valuable data to include in the product label and to support a change to the product's now defunct FDA pregnancy categorization from C (human data lacking; risk in pregnant patients cannot be ruled out) to B (human data reassuring; no evidence of risk in humans). Finally, it provided the Centers for Disease Control and Prevention (CDC) with valuable data with which to update its sexually transmitted disease treatment guidelines.

After the success of the Acyclovir Pregnancy Registry, Burroughs Wellcome implemented several other pregnancy registries, including the Zidovudine Pregnancy Registry in 1989, which evolved into the still ongoing Antiretroviral Pregnancy Registry, as well as the Lamotrigine Pregnancy Registry in 1992, the Sumatriptan Pregnancy Registry in 1996, the Bupropion Pregnancy Registry in 1997, and the Naratriptan Pregnancy Registry in 1997.[2] Other pharmaceutical companies, such as Upjohn,[4] Eli Lilly,[5] and Merck[6] also implemented pregnancy registries.

Beyond pharmaceutical companies, other organizations and academic institutions also implemented pregnancy registries. The National Transplantation Pregnancy Registry was established in 1991 at a university medical center and was designed to study pregnancy outcomes of both male and female transplant recipients.[7] The Antiepileptic Drug (AED) Pregnancy Registry, a multi-drug, multi-sponsor registry in North America, was initiated in 1996 at a university hospital.[8] Since the mid-1990s, several registry-like studies assessing pregnancy outcomes have also been conducted by the Organization of Teratology Information Services (OTIS) and Motherisk.[9,10]

Pregnancy safety studies have evolved greatly over the last 35 years. Most of the early pregnancy registries sponsored by pharmaceutical companies resemble the pregnancy surveillance studies of today. Contemporary pregnancy registries are more scientifically rigorous than pregnancy registries from the 1980s and 1990s. They typically examine multiple maternal and infant outcomes, not just MCMs; and they enroll comparator cohorts to enable sophisticated statistical analyses. Beyond just the scope of the registries expanding, the number of pregnancy registries has grown exponentially. According to the FDA pregnancy registry website,[11] there are currently 125 active pregnancy exposure registries. In addition, other study types are emerging to address some of the inherent limitations of pregnancy registries, including limited sample size and inability to examine relatively rare outcomes. These complementary studies include retrospective database studies, which use existing electronic databases (e.g., insurance claims and/or electronic medical records), population-based case control studies, and population-based surveillance programs or national birth registers.

While pregnancy registries have a long history and are very prevalent, lactation studies are relatively new and much less common. The first FDA-issued PMR for a lactation study was in 2002 for Zelnorm; the next was in 2012 for Linzess. Both studies were milk-only lactation trials to assess concentrations of the products in breast milk using validated assays. In total, the FDA has issued only 15 PMCs or PMRs for standalone lactation studies and nine lactation sub-studies, nested within larger patient registries or studies.[12] Information from lactation studies is valuable to help healthcare providers and lactating patients make decisions about medication use during breastfeeding. When designing and conducting lactation studies, it is

important to minimize the burden on the mother and avoid disrupting the breastfeeding routine.

Regulatory Initiatives Regarding Pregnancy and Lactation Safety Studies in the US

In August 2002, after several pharmaceutical companies had successfully established pregnancy registries, the FDA issued "Guidance for Industry: Establishing Pregnancy Exposure Registries.[13]" This guidance provided a framework for the design of pregnancy registries. It also encouraged biopharmaceutical companies to voluntarily implement pregnancy exposure registries for products with known or suspected risks of fetal harm or products with unknown risks that are likely to be used by patients of childbearing potential.

In February 2005, the FDA issued "Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling.[14]" This guidance provided industry with a framework for the design, conduct, and analysis of data from clinical lactation studies. It also provided guidance on updating labeling to reflect data from these studies.

Both early guidance documents represented the FDA's current thinking on these topics and provided recommendations for how and when to conduct these studies. However, at the time, the FDA did not have the authority to mandate these types of studies.

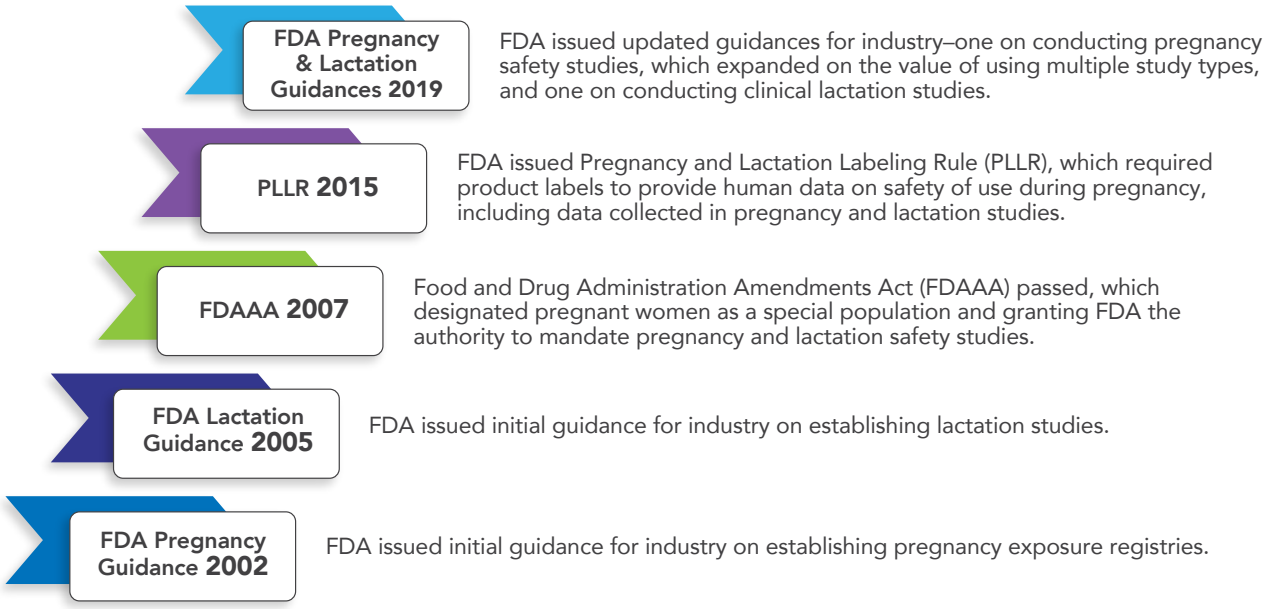
With the passage of the Food and Drug Administration Amendments Act (FDAAA) in 2007,[15] pregnant patients were designated a special population and the FDA was granted the authority to require product manufacturers to conduct post-marketing pregnancy safety studies and lactation studies to assess possible serious risks associated with the products. Post-marketing studies required by the FDA are referred to as post-marketing requirements (PMRs) and post marketing studies that are requested by the FDA are referred to as post-marketing commitments (PMCs).

In June 2015, the FDA's "Pregnancy and Lactation Labeling Rule[16]" (PLLR) was implemented which provides a structured approach to labeling that clearly describes available data to aid in assessing the risk/benefit of a product's use in pregnancy and lactation. The PLLR also specified that product labels should include human data on the safety of product use during pregnancy and lactation. These initiatives provide clear mechanisms for the FDA to require human studies on the safety of product use in pregnancy and lactation.

In response to growing concerns over the lack of scientific rigor in the old-style pregnancy registries and the limitations of pregnancy registries in general, in May 2019, the FDA released "Postapproval Pregnancy Safety Studies: Guidance for Industry.[17]" This guidance provides recommendations on the design of pregnancy registries as well as other complementary study designs to examine the safety of medication use in pregnancy. It is broader than the 2002 guidance, which has since been withdrawn. The guidance stresses the need for more rigorous registry designs, with internal comparator cohorts, systematic data collection, and control for potential confounding. The guidance also stresses the importance of complementary study designs (e.g., retrospective database studies and case-control studies) to help address the inherent limitations of registries alone.

In May 2019, the FDA also issued "Clinical Lactation Studies: Considerations for Study Design: Guidance for Industry.[18]" This guidance outlines considerations for when

Figure 1. FDA Regulatory Initiatives Related to Pregnancy and Lactation Studies



and how to conduct a clinical lactation study and replaces the guidance document issued in 2005.

Figure 1 depicts the various pregnancy and lactation regulatory initiatives implemented by the FDA since 2002.

Figure 2 provides an overview of current pregnancy and lactation study types recommended in the 2019 FDA guidance documents.

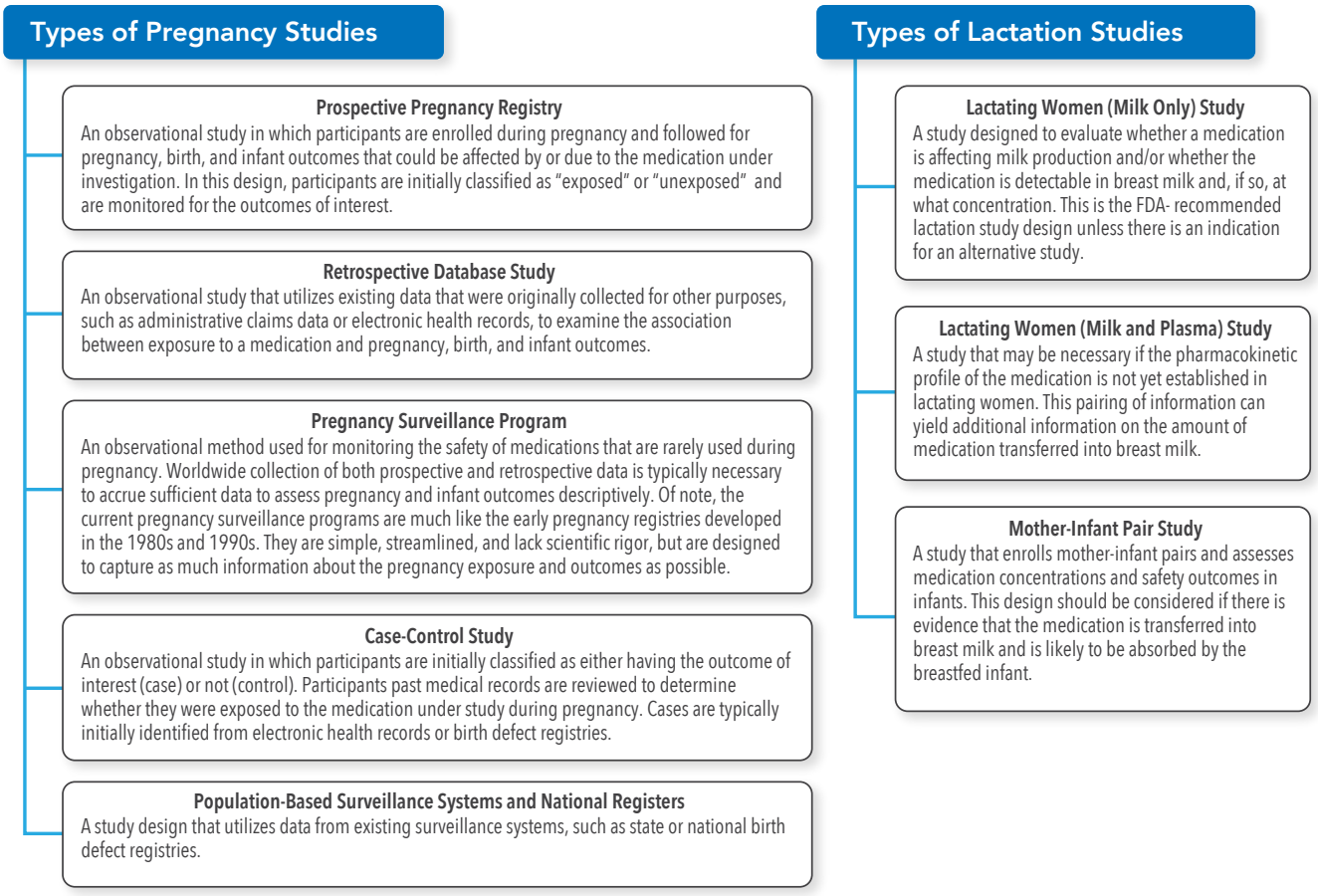
Methods

Under section 506B, Reports of Postmarketing Studies, of the Federal Food, Drug, and Cosmetic Act, the FDA is required to make information on post-marketing studies available to the public. As such, the FDA maintains a publicly available post-marketing requirements and commitments (PMR/PMC) database which is updated quarterly and available on the FDA website.[19] The information in this database comes from product approval letters and annual status reports submitted by new drug application (NDA), abbreviated new drug application (ANDA), and biologics license application (BLA) applicants to the FDA and includes information related to the applicant and product, original approval date, and the specifics of the PMR/PMC. We downloaded the file that became available at the end of July 2021, which covered the time period from 13 August 1947 to 21 May 2021, and reviewed the data to identify PMRs and PMCs for pregnancy and lactation safety studies in humans. Animal studies and clinical trials were excluded.

Pregnancy and lactation PMRs and PMCs were identified by searching the database for "pregna" and "lactat." The description of each identified PMR/PMC was reviewed to confirm that the study met inclusion criteria and categorized it as a pregnancy or lactation safety study. The following data from the database were evaluated descriptively:

- Submission code type (to determine product type: drug, biologic, or vaccine)
- PMR/PMC description
- Original application approval date
- Product name
- PMR authority (to determine obligation type: PMR or PMC)

Figure 2. Pregnancy and Lactation Study Types Recommended by the FDA[17,18]



Sources: US Food and Drug Administration. Postapproval Pregnancy Safety Studies: Guidance for Industry. 2019. Available at: https://www.fda.gov/media/124746/download. Accessed January 28, 2020. US Food and Drug Administration. Clinical Lactation Studies: Considerations for Study Design. 2019. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-lactation-studies-considerations-study-design. Accessed January 28, 2020.

Based on the PMR/PMC description, each pregnancy study was further categorized as either a prospective registry, complementary study, surveillance program, or sub-study (nested within a larger patient registry or study), and each lactation study was further categorized as a milk-only study, multi-focus study, or sub-study (nested within a larger patient registry or study).

We focused on the period from 1998 (the year of the first pregnancy-related PMR/PMC) to 2020 (the last full year of data available). We performed descriptive analyses to:

1. Characterize all pregnancy-related PMRs and PMCs (pregnancy-related PMR/PMC = PMR/PMC for pregnancy or lactation study)
2. Characterize all products for which a pregnancy-related PMR or PMC was issued
3. Determine, by year, the number and proportion of FDA-approved products that had pregnancy-related PMRs or PMCs (and the number of pregnancy-related PMRs and PMCs for each product)

In order to determine the proportion of pregnancy-related PMRs and PMCs among all product approvals, we had to rely on two sources of data. The total number of product approvals for years 1998 to 2007 were obtained from extracting NDA approval data from the FDA's report, titled: "Summary of NDA Approvals & Receipts, 1938 to the present.[20]" This report includes information on approved NDAs by year only; it excludes information on approved ANDAs and BLAs. For the years 2008 to 2020, product approval data were obtained from the FDA's archived website of NDA and BLA Calendar Year Approval Reports.[21] These reports contain descriptive information on NDA approvals, NDA approvals with prior tentative approval, and BLA approvals. Vaccine approvals were excluded from these reports. Denominators were calculated as the sum of all approvals from each year. Since the earlier data (1998-2007) does not include biologics and vaccines, and the later data (2008-2020) does not include vaccines, all prevalence calculations are approximations with the later period being more accurate than the earlier period.

Results

Pregnancy-related PMRs/PMCs

Between 01 January 1998 and 31 December 2020, 1,485 new products were approved by the FDA, of which 113 (7.6%) had at least one PMR or PMC for a pregnancy-related safety study (pregnancy or lactation safety study). Of the 113 products, more than half (51.3%, n=58) were drugs, 35.4% (n=40) were biologics, and 13.3% (n=15) were vaccines. Most products had only one PMR/PMC (n=74, 65.5%, 39 drugs, 21 biologics, and 14 vaccines), whereas 33 products (29.2%) had two or more pregnancy-related PMR/PMCs (18 biologics, 14 drugs, and 1 vaccine), and six products (5.3%) had three pregnancy-related PMR/PMCs (5 drugs and 1 biologic).

For these 113 products, a total 158 pregnancy-related PMRs/PMCs were issued, including:

- 128 PMRs (81.0%) and 30 PMCs (19.0%)
- 142 pregnancy safety studies or sub-studies and 24 lactation studies or sub-studies; note that 8 sub-studies had both pregnancy and lactation components

Figure 3 depicts the proportion of FDA product approvals with pregnancy-related PMRs/PMCs by year. As noted in the figure, the proportion of approved products with at

Figure 3. Proportion of FDA-approved Products With at Least One Pregnancy-related PMR/PMC (Pregnancy or Lactation Study) by Year of Approval and in Relation to Applicable Regulatory Initiatives

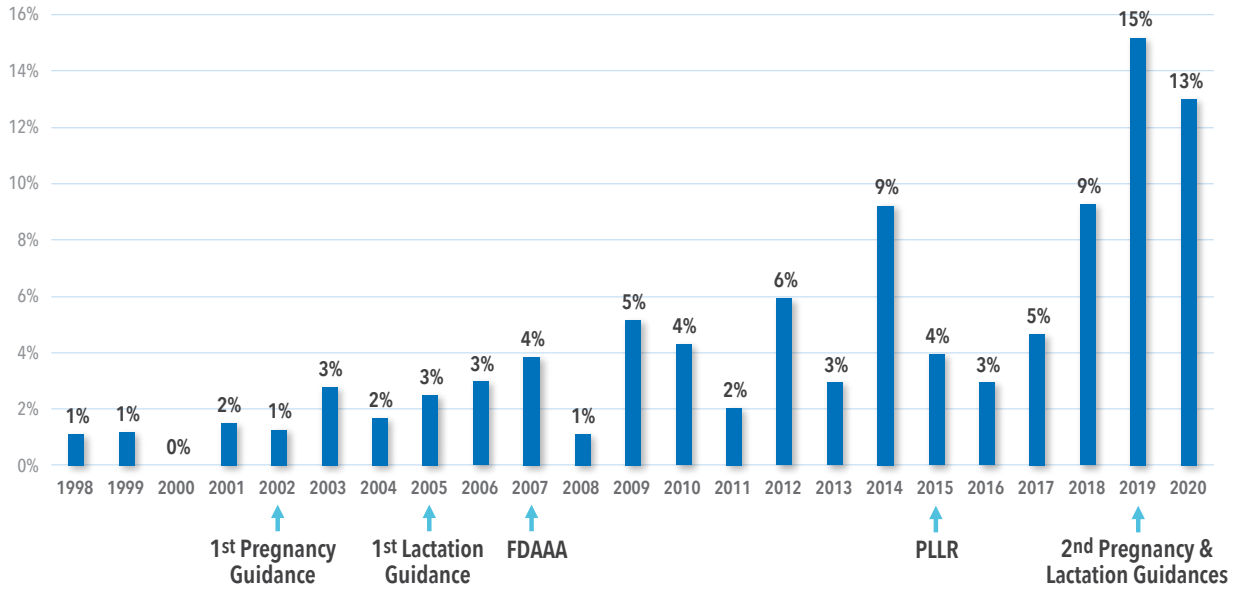
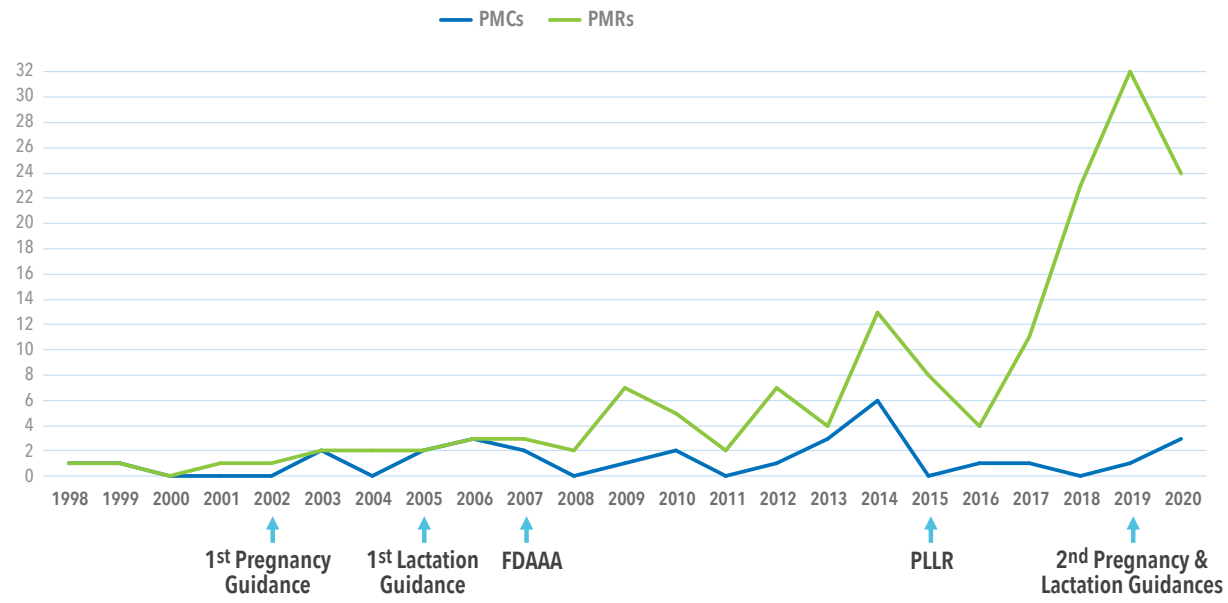


Figure 4. Pregnancy-related PMRs and PMCs by Year and Obligation Type



least one pregnancy-related PMR/PMC increased fairly consistently from 1% in 1998 to 13% in 2020, with a low of 0% in 2000 and a high of 15% in 2019. Over the years, spikes in PMRs/PMCs tended to occur immediately before and after the introduction of applicable FDA regulatory initiatives.

As shown in *Figure 4*, the predominant obligation type has been PMRs since the introduction of the FDAAA in 2007.

As shown in *Table 1*, which is a cross tabulation of product type (drug, biologic, or vaccine) by obligation type (PMR or PMC), 100% of the obligations for vaccine studies were PMCs, whereas most obligations for drugs (97.6%) and biologics (80.0%) were PMRs.

Pregnancy Study PMRs/PMCs

Between 01 January 1998 and 31 December 2020, 106 (7.1%) products approved by the FDA had at least one PMR or PMC for a pregnancy safety study (evaluating maternal, fetal, and infant outcomes after exposure during pregnancy). Of the 106 products, nearly half (48.1%, n=51) were drugs, 37.7% (n=40) were biologics, and 14.2% (n=15) were vaccines. Most products had only one pregnancy study PMR/PMC (n=70, 66.0%, including 34 drugs, 22 biologics, and 14 vaccines), whereas 36 products (34.0%) had two or more PMR/PMCs (18 biologics, 17 drugs, and 1 vaccine).

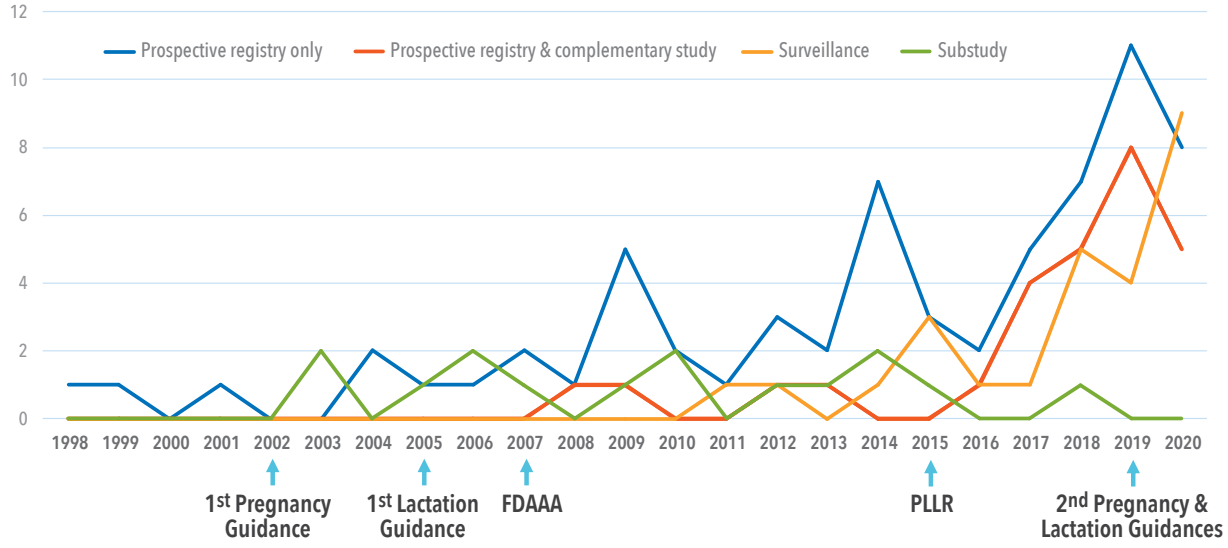
For these 106 products, a total 142 pregnancy safety study PMR/PMCs were required, including 113 PMRs (79.6%) and 29 PMCs (20.4%). All 16 pregnancy safety studies for vaccines were PMCs. The remaining PMCs were for drugs or biologics prior to 2015; from 2015 onward, all studies for drugs or biologics were PMRs.

Figure 5 depicts the number of FDA product approvals with at least one pregnancy study PMR/PMC by study type and year of approval. As shown in the figure, the number of approved products with a PMR/PMC for a prospective registry only has increased fairly consistently since the release of the first pregnancy study guidance in 2002, with spikes over the years that tended to occur immediately before and after the introduction of applicable FDA regulatory initiatives. The figure also shows that over the past five years, there has been an uptick in the number of products with pregnancy surveillance program PMRs/PMCs, and it has become more common for products to have two pregnancy study PMR/PMCs (a prospective registry accompanied by a complementary study). These trends

Table 1. Pregnancy-related PMRs/PMCs by Product Type and Obligation Type

	DRUG (n=82)	**BIOLOGIC** (n=60)	**VACCINE** (n=16)
PMR	80 (97.6%)	48 (80.0%)	0 (0.0%)
PMC	2 (2.4%)	12 (20.0%)	16 (100%)

Figure 5. Number of FDA-approved Products Requiring at Least One Pregnancy Study PMR/PMC by Pregnancy Study Type(s) and Year of Approval



are believed to be directly related to the 2019 guidance document.

Nearly half of pregnancy safety studies were prospective registries (46.5%, n=66), whereas fewer were complementary studies (22.5%, n=32), surveillance programs (18.3%, n=26), or nested studies within a larger patient registry or study (12.7%, n=18). Among the complementary studies, the FDA specified that the study design should be "retrospective" for 11 studies and "complementary" (e.g., retrospective or case-control) for 21 studies. Use of the term "complementary" gained popularity around the introduction of the 2019 guidance on pregnancy safety studies.

Among the prospective registries (n=66), 69.7% were PMRs (n=46) and 30.3% were PMCs (n=20). The first prospective registry PMC was in 1998 and the first PMR was in 2001. In 2020, 62.5% of prospective registries were PMRs (n=5). Among all prospective registry PMRs/PMCs, 40.9% (n=27) were for biologics, 36.4% (n=24) were for drugs, and 22.7% (n=15) were for vaccines. All studies for drugs were PMRs (n=24), most studies for biologics were PMRs (81.5%, n=22), and all studies for vaccines were PMCs (n=15).

Nearly all complementary studies were PMRs (96.9%, n=31). The first complementary study was a retrospective study PMR in 2008. The only complementary study PMC occurred in 2013 (for the only vaccine ever to require a complementary study), and every year since then, 100% of complementary studies have been PMRs. Among all complementary PMRs/PMCs (n=32), 56.3% (n=18) were for drugs, 40.6% (n=13) were for biologics, and 3.1% (n=1) was for a vaccine. Starting in 2017, complementary study PMRs became common, with multiple approved products per year having this type of FDA requirement. Between 2017 and 2020, a total of 26 approved products had a PMR for a complementary study.

All surveillance programs were PMRs (n=26), of which the majority were for drugs (80.8%, n=21) and 19.2% were for biologics (n=5). The first surveillance program was in 2011, and between 2018 and 2020, a total of 18 approved products had a PMR for a surveillance program.

Just when pregnancy surveillance programs were becoming common, pregnancy safety sub-studies, nested within larger patient registries or studies, started declining. The first nested pregnancy safety studies were in 2003, and the most recent nested studies were in 2018. Among the 18 PMR/PMCs for pregnancy safety sub-studies, 55.6% were PMRs (n=10) and 44.4% were PMCs (n=8). The majority were for biologics (72.2%, n=13) and 27.8% (n=5) were for drugs. Eight of the 18 PMR/PMCs for pregnancy safety sub-studies indicated within the same PMR/PMC that a lactation sub-study was also required.

Lactation Study PMRs/PMCs

Between 01 January 1998 and 31 December 2020, 24 (1.6%) products approved by the FDA had one PMR or PMC for a lactation safety study (evaluating breast milk concentrations and/or infant outcomes). Of the 24 products, 62.5% (n=15) were drugs and 37.5% (n=9) were biologics. All products had only one lactation study PMR or PMC; 16 with a PMR (66.7%) and 8 with a PMC (33.3%). Nearly all drugs with a lactation study obligation had a PMR, whereas most biologics had a PMC.

The first lactation study obligation was a milk only PMR for a drug approved in 2002. In all years since then, between 0 and 2 approved products had a lactation study PMC or

PMR, except in 2019 (the year of the most recent lactation guidance) when 7 products had a lactation study PMR. All lactation study obligations for products approved after 2014 were PMRs.

Among the lactation safety study PMR/PMCs (n=24), 13 (54.2%) were rigorous milk only studies (to quantify the concentrations of products in breast milk), 2 (8.3%) were multi-focus studies (to assess both the concentrations of products in breast milk and infant outcomes), and 9 (37.5%) were lactation sub-studies, nested within larger patient registries or studies.

Of the milk only lactation studies (n=13), nearly all were PMRs for drugs (92.3%, n=12) and only 1 (7.7%) was a PMC for a biologic. Nine of the 13 milk only lactation studies were PMRs for drugs approved in 2015 (the year of the PLLR) or later.

Of the multi-focus lactation studies (n=2), both were PMRs for drugs approved in 2019. Of the nine lactation sub-studies, the majority were PMCs (77.8%, n=7) and nearly all were for biologics (88.9%, n=8). Eight of nine of these studies had both a pregnancy safety and lactation safety component and did not assess breast milk concentrations of the products of interest. One of these studies (a PMR) focused only on lactation safety and additionally quantified breast milk concentrations; however, this product also had two separate nested pregnancy safety study PMRs.

Conclusion

Pregnancy safety studies have evolved greatly over the last 35 years. Early pregnancy registries resembled the pregnancy surveillance studies of today; whereas contemporary registries are more scientifically rigorous (i.e., examine multiple maternal and infant outcomes, enroll comparator cohorts, and employ sophisticated statistical analyses). The proportion of approved products with at least one pregnancy-related PMR/PMC has increased fairly consistently since 1998 with a low of 0% in 2000 and a high of 15% in 2019. Over the years, spikes in PMRs/PMCs tended to occur immediately before and after the introduction of applicable FDA regulatory initiatives.

Since the first pregnancy study guidance in 2002, the number of approved products with a PMR/PMC for a prospective registry only has increased; and over the past five years, there's been an uptick in the number of products with pregnancy surveillance program PMRs/PMCs and with two pregnancy study PMR/PMCs (a prospective registry accompanied by a complementary study – either retrospective database study or case-control study). These trends are believed to be directly related to the 2019 guidance document.

Since the first lactation study PMR in 2002, very few approved products had lactation study PMRs/PMCs until 2019, when seven products had a lactation study PMR. This trend is believed to be directly related to the lactation guidance released that year.

Based on the content and findings outlined in this paper, continuing attention on pregnancy and lactation studies by the FDA is expected, along with associated increases in safety studies. Understanding these changing dynamics and planning for potential pregnancy safety studies prior to product approval can help companies be prepared for any potential requirements or commitments the FDA may ask of them. ■

For more information, please contact info@evidera.com.

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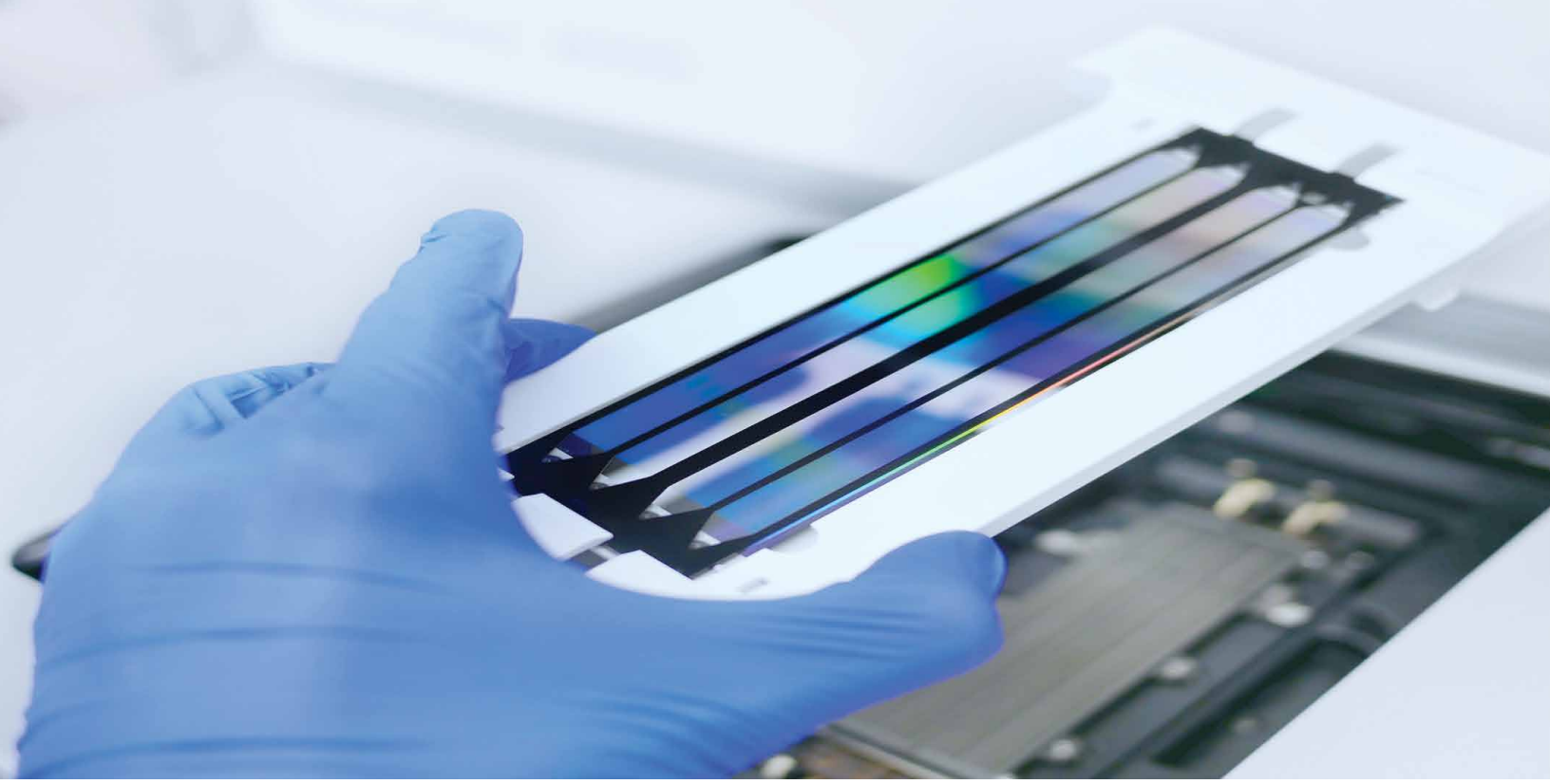


Reimbursement Landscape for NGS in Oncology in Australia, Canada, and the United States

David January, PhD, MWC
Associate Scientific Director
Evidence Synthesis, Modeling & Communication
Evidera, a PPD business

Introduction to NGS

The term "next-generation sequencing" (NGS) refers to a variety of technologies that allow for rapid, high-throughput genetic sequencing.[1,2] NGS technologies allow for much faster, less expensive sequencing of the genes in a sample than the conventional Sanger sequencing technique, which is restricted to sequencing specific genes one at a time.[1,3] NGS also allows for the identification of multiple allelic variants (alternate forms of the same gene) simultaneously, whereas only one allelic variant can be identified per sequencing run when using older sequencing methods.[1] NGS technologies achieve this increase in speed and identification of allelic variants by fragmenting DNA into shorter strands of base pairs and performing the sequencing reaction for each fragment simultaneously.[2]

The decreased cost and potential for rapid whole genome sequencing afforded by NGS technologies has many potential applications in healthcare. One area of use is in newborn screening for genetic diseases.[4-6] NGS has been widely used to determine whether newborns have genetic variants associated with lysosomal storage disorders and other inborn errors of metabolism, allowing for potentially earlier diagnosis and treatment to avoid the progressive clinical deterioration, disability, and, ultimately, mortality resulting from these diseases if left untreated.[5] NGS can also be used to diagnose genetic diseases after patients present with clinical manifestations, and the ability to target multiple allelic variants simultaneously may help reduce the sometimes long and difficult diagnostic journey for patients who present with symptoms associated with several differential diagnoses.[2,5]

David January

Another area of focus for the use of NGS technologies has been oncology. NGS can be used to test for germ-line mutations to establish a patient's risk for developing certain cancers, such as with the *BRCA* mutation.[7] NGS can also be used in a complementary fashion to assess cancerous tissue directly for certain genetic mutations that might predict response to certain anti-cancer agents, such as for del(17p) chronic lymphocytic leukemia (CLL).[2,8,9] This latter use is the focus of this paper. As of 2017, most oncologists in the United States (US) reported relying on NGS tests when making decisions relating to treatment for their patients.[10] Further, several of the newer oncology therapeutics being released are very targeted for specific mutations and do not work well for tumors with different genotypes (for example, Herceptin's indication in HER2 overexpressing tumors or tumors with HER2 gene amplification).[11] Foundation Medicine maintains a list of over 20 such therapies at their website: https://www.foundationmedicine.com/test/foundationone-cdx. As these newer, powerful, targeted treatments are typically very expensive,[12] NGS may be useful in identifying those patients who are most likely to benefit from the treatments and avoid inefficient healthcare spending. This recognition of the usefulness of NGS in guiding treatment decisions for patients with cancer, and the potential to make use of these targeted therapies economically feasible, highlight the urgency of the question of how these tests can gain reimbursement and wider use. This paper explores this question.

Key Questions for This Paper

In this paper, we examine the following questions relating to the use of NGS in oncology:

- How are NGS diagnostics being assessed and reimbursed in different markets (Australia, Canada, and the United States [US])?
- What evidence do manufacturers need to generate to promote favorable reimbursement?

Assessing NGS Tests for Reimbursement

Across payer systems, several key concepts are relevant to the determination of whether NGS diagnostics, or any diagnostic, will achieve reimbursement:[13]

- Analytical validity, or the ability of the diagnostic to detect the presence or absence of the biomarker of interest
- Clinical validity, or the relationship between the presence of a gene variant and the presence or risk of a disease
- Clinical utility, or the impact of the test results on clinical decision making related to patient care and prevention of disease
- Cost and/or cost effectiveness

While these concepts recur across payer systems, the specific methods of analysis and definitions vary, and ethical or social considerations may be incorporated into the evaluation as well.[13]

Graphic 1. Concepts for Reimbursement Assessment of NGS Tests

Analytical Validity	Can the test detect the targeted gene?
Clinical Validity	Does the targeted gene reliably predict disease?
Clinical Utility	Does the test inform diagnosis or treatment?

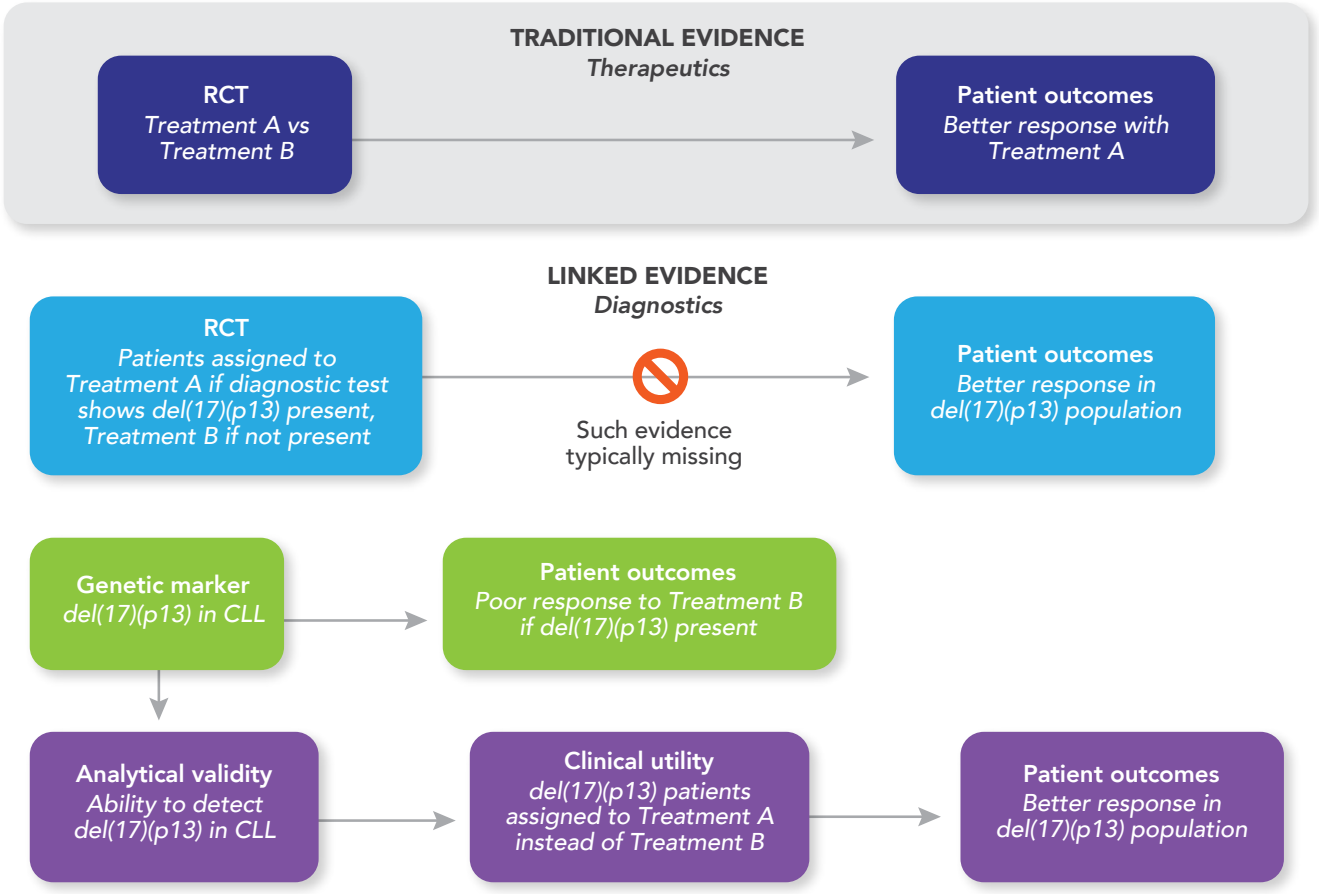
For diagnostic tests, often there is no direct clinical trial evidence of the impact of the test on patient outcomes.[14] In situations like these, decision makers often rely on evidence linking the use of the test to clinical outcomes.[14] For example, in CLL, the del(17)(p13) mutation is associated with poor response to traditional chemotherapy, and there is high quality, randomized controlled trial (RCT) evidence that certain newer treatments continue to be effective in these patients.[8] In light of these facts, payer decision makers may link the evidence about the analytical validity of the test (that is, the ability to reliably identify del(17)(p13) variant) to the already established evidence on the clinical validity of that variant (the evidence of poor response to traditional treatment) and the evidence on the improved outcomes under alternative treatment to establish clinical utility (see *Graphic 2*).[14] Thus the evidence burden may be somewhat reduced for manufacturers seeking reimbursement for NGS tests if there is already a body of literature establishing the relation between the presence of a variant and prognosis. The evidence burden will likely vary by the nature of the test: payers will want evidence for multiple tumor types if reimbursement for the use of the test is being sought in multiple tumor types.

In the sections that follow, recent decisions and guidance from Australia, Canada, and the US are summarized and presented as case studies to illustrate how these payers are making decisions relating to NGS and provide concrete examples of the types of evidence that manufacturers may need to generate to secure reimbursement.

Australia

In Australia, the Department of Health's National Health Genomics Policy Framework and Implementation Plan 2018-2021 presupposes that any test being used has demonstrated analytical validity, clinical validity, and clinical utility when they are accredited by the National Association

Graphic 2. Traditional vs Linked Evidence



of Testing Authorities/Royal College of Pathologists of Australasia and validated with the Therapeutic Goods Administration.[15,16] The Framework then stresses the cost effectiveness of NGS diagnostics as a key consideration for ensuring appropriate allocation of healthcare resources.[16]

The reimbursement for genetic tests in Australia involves multiple payers, including the national Medicare service and also private insurance companies and local hospitals, depending on the circumstances.[17] To obtain reimbursement from Medicare, the diagnostic must go through the Medical Services Advisory Committee process, which evaluates the clinical validity, clinical utility, and cost effectiveness of the diagnostic.[17]

Studies such as those completed by Wong 2015 and Gordon 2020 provide the type of evidence sought here. Wong and colleagues performed NGS on samples from 854 patients in Victoria, Australia.[18] Of these patients, 534 (63%) were found to have clinically relevant mutations; of these, 222 (26% of the overall sample) exhibited mutations that indicated whether an approved or pre-clinical drug would be especially effective or ineffective in treating their cancer.[18] This study, then, demonstrates the clinical utility of the NGS diagnostic in determining treatment for patients with cancer. Gordon and colleagues collected cost information for a variety of NGS diagnostics used in diagnosing patients in Brisbane, Australia, with a variety of different cancers.[19] While this paper did not perform an analysis of cost effectiveness, collection of costs of this nature are a step toward the cost-effectiveness analysis that would be needed. As of May 2021, NGS for use in cancer had not been approved for reimbursement in Australia through the Medicare Benefits Schedule.[20]

Canada

Diagnostics are assessed in Canada by the Health Technology Expert Review Panel (HTERP),[21] a division of the Canadian Agency for Drugs and Technologies in Health (CADTH), which uses a multi-criteria decision framework that assesses the need for the technology, the benefits, the harms, patient preferences, economic impact, and considerations from several other domains to determine whether a technology should be reimbursed.[21] NGS technologies have received preliminary guidance in A Rapid Response Report from CADTH issued in 2014.[22] This report posed the question "what is the cost effectiveness of next-generation sequencing?" as one of the core research questions to be addressed by the report,[22] suggesting that, similar to Australia, Canada is looking to incorporate NGS into the existing framework for evaluating health technologies. The report conducted a systematic literature review looking for comparisons of NGS versus other

sequencing techniques that reported cost-effectiveness outcomes and found the literature at the time to be lacking clear evidence addressing this question.[22] Notably, the report calls out the (at the time) high rate of false-positive findings for deleterious variants as a limitation for the use of NGS technologies;[22] this perception of decreased analytical validity versus Sanger sequencing must be overcome for NGS to gain greater market share.

Since 2014, additional programs and guidance for genetic technologies have been developed in Canada. Specifically, Canada has rolled out the CADTH process for drugs with expanded health system implications[23] and the CADTH review process for cell and gene therapies.[24] Under the first process, health technologies that have the potential for "substantial system-wide implementation challenges" may apply to undergo a separate evaluation process which assesses the broader impacts on the healthcare system and seeks greater stakeholder engagement.[23] Under the second process, manufacturers of cell and gene therapies may apply for special review that incorporates broader ethical and implementation considerations than the standard review.[24] Part of this application must include budget-impact analysis from a pan-Canadian perspective of the new technology.[24] While both of these new processes are focused on drugs or therapies, they reflect a recognition in Canada that advanced health technologies relying on genetic information require special consideration. It therefore seems likely that such considerations would factor into the assessment of any NGS diagnostics.

A review by Weymann and colleagues published in 2019 found that economic evidence for NGS in Canada is improving since the 2014 Rapid Response Report.[25] In a structured literature review from 2005 to 2018, 25 references were identified that met the inclusion criteria. The included studies assessed resource utilization, cost-consequence analysis, and cost-effectiveness analysis. NGS tests were found to be cost effective at willingness-to-pay thresholds of $50,000 to $100,000 per life-year gained or quality-adjusted life year. More evidence of this sort will be needed to help guide payer decision making in Canada. Weymann and colleagues noted that evidence that properly accounts for all NGS outcomes, both health outcomes (such as changes to treatment and survival) and non-health outcomes (such as the value individuals place on knowing their risk profile), is difficult to develop but essential to estimate the true cost effectiveness of NGS diagnostics. They also note that greater consistency in assessing cost effectiveness and reduced uncertainty in the results are needed to help payer decision making.

US

In the US multi-payer system, coverage for NGS panel tests is widely variable and dependent on a range of factors, including payer type (public or private). Within private payers, there is also variation in coverage decisions, notably related to the size of the plan, among other factors.[26]

> … these aspects of the decision-making process show a crucial role for clinical validity and clinical utility in determining the reimbursement for these tests. Notably, CMS does not examine societal costs and benefits when reaching coverage determinations.

The largest US payer is the publicly funded Centers for Medicare and Medicaid Services (CMS). In 2018, CMS issued a favorable national coverage determination (NCD) for NGS testing in patients with recurring, relapse, refractory, or advanced metastatic solid tumors.[26,27] This NCD was updated in 2020 to cover NGS testing for patients with suspected hereditary breast and ovarian cancers, regardless of stage.[27] Notably, in their decision, CMS stipulated that the NGS test must be either (a) approved by the FDA (typically achieved as a companion diagnostic evaluated alongside a precision medicine therapy[28]) or (b) approved by regional Medicare administrators via a local coverage determination (LCD).[27] These stipulations indicate that CMS is starting from a position of presumed analytical validity. To reach its coverage determination, CMS relied on a systematic literature review yielding 24 studies.[27] It is important to note that many NGS tests conducted in the US are not approved by the FDA.[29] Instead, NGS panels are frequently developed, owned, and performed by individual laboratories.[29] The quality of these tests is assured by oversight and certification from the Clinical Laboratory Improvements Amendments (CLIA).[27] Thus, many patients who would seek NGS testing as part of an informed cancer treatment strategy may not be granted access by CMS if providers choose to order one of the many tests that are regulated under CLIA as opposed to the FDA. Such laboratory-developed tests must be approved by local Medicare administrators,[27,29] which introduces opportunity for regional variation in the proportion of qualified patients who receive testing. In addition, the burden of determining whether there is a favorable LCD in place for a specific test could serve to limit access to NGS testing.

The studies from the systematic literature review by CMS established the clinical validity of the test by demonstrating the association between the presence of the variant gene and the development of disease and examined the relationship between genotype and prognosis and response to treatments.[27] Additionally, the NCD requires the results of the test specify treatment options.[27] Together, these aspects of the decision-making process show a crucial role for clinical validity and clinical utility in determining the reimbursement for these tests. Notably, CMS does not examine societal costs and benefits when reaching coverage determinations.

The NCD gave rise to the question of whether private payers would consider the CMS position when making their own decisions about NGS coverage.[26,29] A recent study by Trosman et al. determined that 33 of 69 payers (48%) with explicit policies regarding the use of NGS in sequencing tumors had positive coverage in April 2019, compared with a single payer in November 2015. Just under half of payers (48%) initiated positive coverage in the 17 months following the NCD, whereas 52% had initiated positive coverage in the 25 months preceding the NCD.[26] These data indicate that US private payers did not universally wait for CMS to cover NGS before doing so themselves. While the faster rate of coverage of NGS by private payers following the NCD is suggestive, it could also be related to other factors, such as maintaining competitiveness with other private payers.

In contrast to the CMS requirement, none of the adopters in the study had made FDA approval of NGS as a companion diagnostic a prerequisite for reimbursement.[26] Of the 33 payers with favorable NGS coverage, most (67%) had a general, National Comprehensive Cancer Network (NCCN) guideline-dependent policy. Twenty-one percent of adopters covered NGS testing for non-small cell lung cancer (NSCLC) only, and 79% covered testing across multiple cancer types, either listing specific cancers or referring to the NCCN guidelines.[26] Inclusion in guidelines may be seen by private payers as establishing the analytical and clinical validity as well as clinical utility of the tests. Thus, developers of NGS tests who are not positioned to receive FDA approval via the companion diagnostic route, whether due to cost, time, or operational constraints, may wish to consider guideline outreach as an alternative strategy for gaining reimbursement. The Trosman study did not indicate whether cost or cost effectiveness of the tests was performed by the private payers.

Conclusions

For targeted use of the newer, more powerful anti-cancer treatments, NGS technology is essential and must be made widely available. Use of NGS will enable the identification of the genetic variants associated with an individual's cancer and, through avoiding repeated testing for single variants and avoiding use of less effective treatment, should result in efficient use of healthcare resources while simultaneously improving health outcomes.[30] NGS also helps avoid issues previously seen with sequential testing due to the limited amount of tissue available from tumor biopsy and may avoid the need to harvest additional samples, thus potentially reducing patient and healthcare system burden. In this brief review of how some markets are reimbursing NGS technologies, we have seen that manufacturers of these diagnostic tests will need to be able to demonstrate the analytical validity, clinical validity, and clinical utility of their tests[13] to support positive reimbursement decisions in the US and as part of developing the data to illustrate cost effectiveness in Australia and Canada. ■

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For more information, please contact info@evidera.com.

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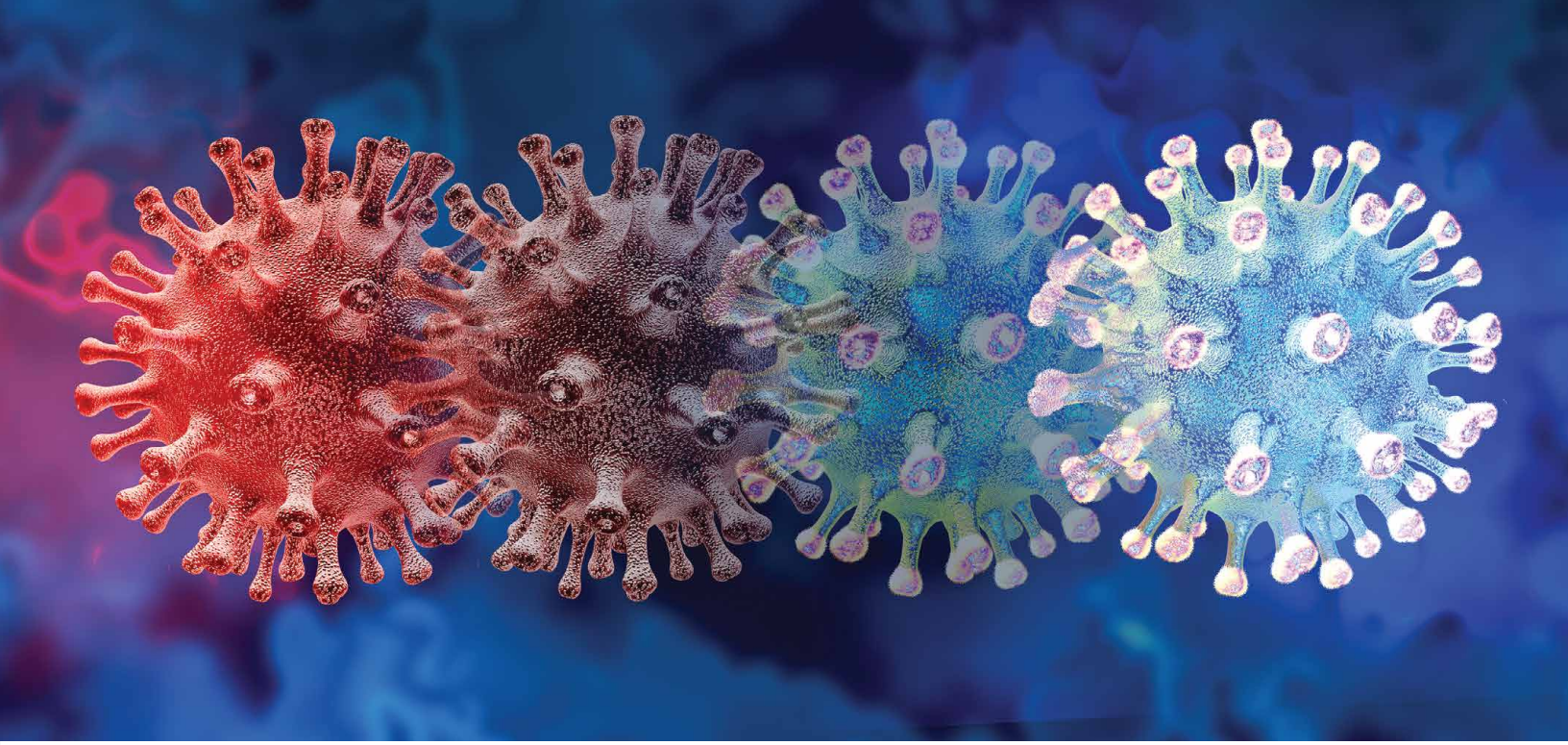


Emergence of SARS-CoV-2 Variants, Surveillance Data Availability, and the Impact on Prediction Models

Lindsey Wilson, BS
PPAS Data Collection, Real-World Evidence
Evidera, a PPD business

Payal Pozin, MPH
Research Associate III, Real-World Evidence
Evidera, a PPD business

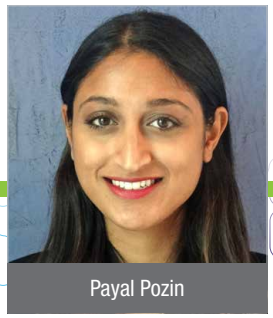
Margaret Richards, PhD, MPH
Senior Research Leader, Real-World Evidence
Evidera, a PPD business

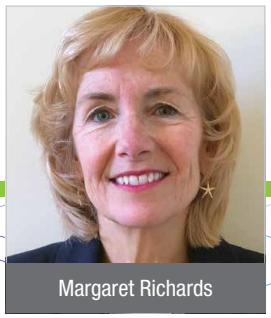
Ben Greener, MS, PharmD
Senior Director, Clinical Science, Strategic Development Consulting
PPD

Selective Pressure Drives the Emergence of New SARS-CoV-2 Variants

Viruses are infectious biological agents that, in their most basic form, consist of a protein coat that encapsulates genetic information as either DNA or RNA. Once a virus enters a host, its primary function is to replicate while escaping clearance by immune mediated mechanisms. Effective replication may lead to more transmissible particles being shed, greater spread to other hosts, and continued survival. Given that viruses tend to travel light due to their limited size, they must rely at least partly on host machinery for their replication and spread. Viruses therefore hijack host cellular machinery to assist in making copies of their genetic information and producing the proteins that their genome encodes. The more a virus circulates in a population, the more likely it is that *errors* will be made while replicating its genome, resulting in


Lindsey Wilson


Payal Pozin


Margaret Richards


Ben Greener

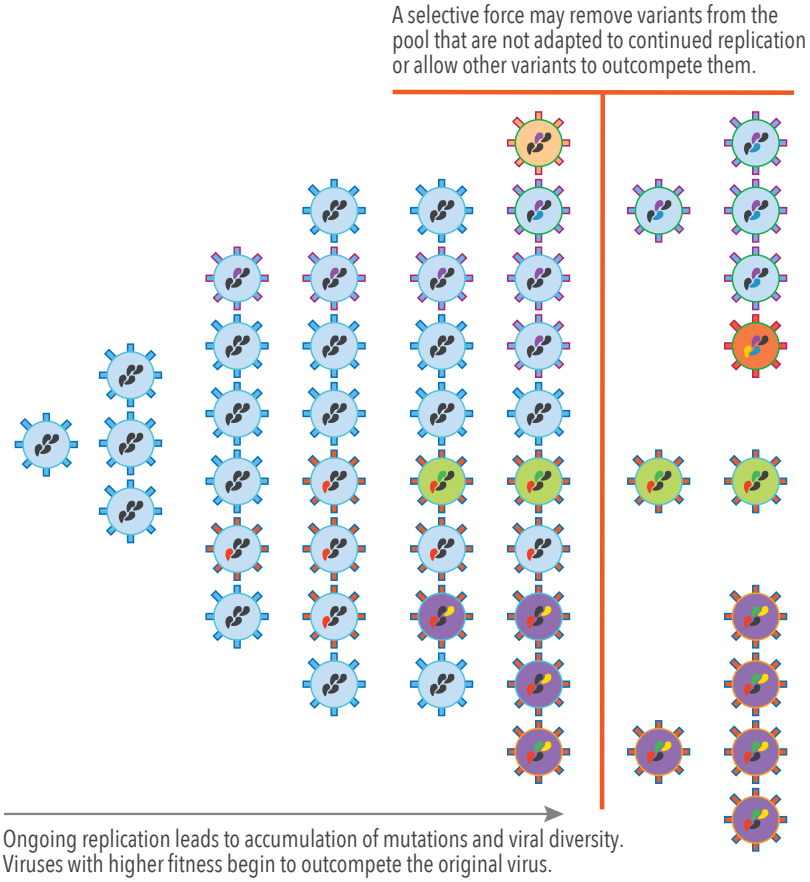
lasting changes to its genetic material – otherwise known as mutations. These "errors" can be due to the natural error rate from polymerases in the host or may be mediated by specific viral mechanisms that accelerate this process, depending on the virus.[1] As the cycle of replication is short for most viruses, these mutations can occur rapidly due to the sheer volume of progeny being produced. Further, these mutations continue to accumulate over time as more replication cycles occur for a genome that has already been altered from its original sequence. Changes in the genetic code of a virus can result in structural changes to the encoded viral proteins that may alter the set of observable characteristics of the virus, such as transmissibility, clinical presentation or progression, efficiency of replication, or pathogenicity. Sometimes, mutations emerge with no impact on the viral protein sequence; these are regarded as *silent mutations*. Other times, changes in the amino acid sequence alter how the virus behaves and may give the virus either an evolutionary boost over its siblings or alternatively, may be detrimental to replication and survival. These accumulated mutations can confer an increase or decrease in the overall *fitness* (a comparative measure of survival advantage) of that virus and may lead to dominance for viruses with a substantial advantage. Throughout the SARS-CoV-2 pandemic, we have already observed that this evolutionary boost may result in increased transmission, evasion of natural immune response or neutralizing antibodies, and other phenotypes that impact public health and social policy requirements.[2] The key to reducing viral mutations is simple: limit the host reservoir and therefore viral proliferation. This is achieved by decreasing transmission through policy and reducing the potential for effective replication through vaccination.

SARS-CoV-2, the virus that causes COVID-19, has been circulating worldwide since early 2020. Since the start of the pandemic, scientists and public health officials have been actively monitoring the evolution of the SARS-CoV-2 virus through genomic surveillance (the process of decoding the genomic sequence of the virus in clinical isolates and observing how it changes over time). Genomic surveillance helps public health officials track the path of the pandemic and identify mutations of concern. SARS-CoV-2, during its widespread transmission and replication throughout the pandemic, has gone through countless replication cycles resulting in many accumulated changes, which are continuously subjected to a range of selective forces that allow for new variants to emerge and gain dominance. This process, Darwinian evolution, is caused by natural selection acting upon variations of mutations, resulting in the selection of mutations that make the virus more fit to compete, survive, and reproduce.

For viruses, this selection process is well characterized and can be replicated in a laboratory by various approaches including the application of selective pressure in experimentally infected cell cultures.[1]

In the early stage of the COVID-19 pandemic (late January to early February 2020), scientists identified the D614G mutation, a problematic change to the genomic sequence at the 614th amino acid position of the spike protein, where the amino acid aspartate (D) was supplanted by glycine (G).[3] This change to the spike protein resulted in enhanced viral loads in the upper respiratory tract that may have increased viral shedding and therefore transmissibility.[4-6] When mutations such as D614G make a virus more transmissible, the mutated virus will continue to proliferate and eventually become more prevalent among the population at large, competing with other variants of the virus and crowding out less transmissible variants. As of June 2020, the D614G mutation was identified in nearly all SARS-CoV-2 samples worldwide and was present in dominant circulating viruses along with other mutations.[7] It is important to note that while a single mutation can certainly generate a new phenotype, the stepwise process of accumulating mutations and the sum impact of these changes can profoundly change the behavior of a pathogen. We can group sets of these changes into viral *clades* and *lineages*. These biological terms are ways to classify groupings and genetic

Figure 1. Genetic Drift and Selective Forces During Viral Replication



relationship. A **clade** is a genetic grouping that can be traced back to a single ancestor while a **lineage** refers to a continuous line of descent within a clade. Grouping mutated virus sequences by lineage is helpful at the front edge of the pandemic, during outbreak investigations, or when tracking patterns on a more granular scale. Lineage classification takes external information into account, such as details on how the virus is spreading and the genetic sequence data. What we now refer to as the "Alpha Variant" or "Delta Variant" are actually described by lineages – specifically, lineage *B.1.1.7* and *B.1.617.2*.

In addition to increased transmissibility, there are a number of reasons why specific variants become increasingly dominant in the viral pool. Some combinations of mutations may allow the virus to escape the activity of neutralizing antibodies or drugs due to a structure change in a viral epitope or decreased affinity at the target site for small molecule therapeutics. In some cases, specific mutations may assist viruses in overcoming natural immunity or therapeutic or prophylactic interventions. This is because only viruses that can escape immune detection or avoid neutralization are able to replicate effectively so a selective pressure is introduced. Such a scenario is a risk among vaccinated individuals, who may inadvertently be amplifying more virulent pathogens or resistant pathogens by suppressing proliferation of competing viruses that are more susceptible. It is important to understand that while this type of selection is possible in vaccinated individuals, the burden of mutation created in individuals who are not vaccinated is far higher since replication may occur at higher levels. The process of viral evolution is the reason why it is so important for an entire population to get vaccinated, as opposed to only a portion of the population, in order to decrease infections worldwide and slow the emergence of new variants that may be able to overcome the barrier of vaccination and therapeutics. While it is expected that new variants of SARS-CoV-2 that pose an increasing risk to humans will continue to emerge, continued genomic surveillance and prediction tools will help mitigate this risk.

Classification of COVID-19 Variants by Clinical Impact[8]

Public health officials have been monitoring the genomic sequence of the SARS-CoV-2 virus since the onset of the pandemic. It was not until the end of 2020 that the emergence of variants that posed an increased risk to global public health were clearly identified. This prompted the classification of variants into three categories: Variants of Interest (VOIs), Variants of Concern (VOCs), and Variants of High Consequence (VOHCs).[8] Fortunately, none of the current variants have yet been classified in the latter category. However, there are a number of variants which are now regarded as VOIs and VOCs, and it is important to monitor these to inform the ongoing public health response to the COVID-19 pandemic. The distinction between these classifications is based on expected impact and level of evidence. Variants of Interest have specific genetic markers that may result in phenotypic changes that are associated with factors including but not limited to predicted immune escape, treatment resistance, or potential for increased transmissibility or more severe disease.[8] VOIs are reclassified as VOCs when there is evidence of these phenotypic changes and therefore a likely epidemiological or clinical impact.[8] VOHCs are variants with established evidence to support more severe clinical disease outcomes, diagnostic failures, or significantly reduced effectiveness of prophylactic or therapeutic interventions. Table 1 provides a summary of key mutations identified in currently circulating variants.[8]

Variant Data Availability and Prediction Models

Many different forecasting models that predict the spread of COVID-19 have been developed in response to the COVID-19 pandemic. Models include predictions of COVID-19 cases, deaths, and hospitalizations by geographic locations. Most of the models that currently exist use mathematical or epidemiological techniques that incorporate basic parameters to determine the spread of disease.[9] The parameters, inputs, outputs, data sources, and modeling methodology are critical components to each model, and if stated clearly, can support decision making and the formulation of health policy to help in the fight against the disease. Besides public behavior and policy, one of the most important parameters in this pandemic is transmissibility which is enhanced by the accumulation of mutations.

One of the biggest challenges in estimating these models' parameters is access to comprehensive, quality, and real-time data on the COVID-19 epidemic. The Johns Hopkins University Center for Systems Science and Engineering (JHU CSSE) is one example dataset that combines multiple data sources from around the world that serves as a COVID-19 data repository and includes data on confirmed cases, deaths, recovered cases, and active cases by granular geographic region. The JHU CSSE COVID-19 data is publicly available, updated regularly, and helps inform modeling efforts and public health control measures.[10] With the rise in cases attributed to newer VOCs such as Delta (lineage B.1.617.2), modelers are on the hunt for publicly available, timely, downloadable data on COVID-19 case counts by VOC and granular geographic location. Multiple organizations, such as *The New York Times* and GISAID collaborators, offer visual representations of the VOC data by granular geographic location, however, the data are not downloadable. Other organizations such as the European Centre for Disease Prevention and Control (ECDC) share these data but only at the country level and limited to Europe. Only one GISAID collaborator, the Research Center at the King Abdullah University of Science and Technology (KAUST), has developed a COVID-19 virus mutation tracker system (CovMT).[11] The downloadable KAUST data shows the mutation fingerprint (individual genomic data of SARS-CoV-2 isolates characterized by a specific set of mutations compared to original isolate), the number of COVID-19

Table 1. Key Mutations Identified in Selected Variants

World Health Organization Designation	Lineage	Spike Protein Mutations
Alpha	B.1.1.7	69del, 70del, 144del, (E484K), (S494P), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N)
Beta	B.1.351	D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V
Gamma	P.1	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I
Delta	B.1.617.2	T19R, (G142D), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N
Epsilon	B.1.427, B.1.429	(S13I), (W152C), L452R, D614G
Zeta	P.2	E484K, (F565L), D614G, V1176F
Eta	B.1.525	A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L
Iota	B.1.526	(L5F), T95I, D253G, (S477N), (E484K), D614G, (A701V)
Kappa	B.1.617.1	(T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H
Lambda	C.37	G75V, T76I, R246-G252del, L452Q, F490S, D614G, T859N
Mu	B.1.621, B.1.621.1	T95I, Y144T, Y145S, Y146insN, R346K, E484K, N501Y, D614G, P681H, D950N
N/A	B.1.617.3	T19R, G142D, L452R, E484Q, D614G, P681R, D950N

cases attributed to the mutation, and global granular geographic location. Epidemiologists continue to stress the importance of having a collective, international, and public COVID-19 database in order to respond to the outbreak in a timely manner.[12] Such data are critical in determining the need for hospital resources, and for informing federal and local public health decisions as well as drug development.[9] As the pandemic continues to evolve, these predictive models must adapt to include new data such as the relative mix of variants and other factors that impact infection and transmission rates,[13] such as variant specific transmissibility and vaccine distribution. However, just like viruses, scientists will need to rely on publicly available "data hosts" to survive and manage these pandemics.

The path to end the pandemic will require scientists, public health officials, stakeholders, policy makers, and communities to collaborate and unify around shared goals and objectives, such as limiting transmission of the disease and minimizing impact on countries with limited preparedness capacity. Unified and informed policy decisions supported by accessibility of publicly available COVID-19 data could help achieve the same goal of ending the pandemic. Outside of human behavior and public policies, the most influential parameters that will change the trajectory of the COVID-19 pandemic is the evolution of new variants, immune escape, and waning immunity.[14] With clear public health messaging and continued advances in our understanding of the virus, the goal is to limit the host space that SARS-CoV-2 has to proliferate and evolve within. ■

For more information, please contact info@evidera.com.

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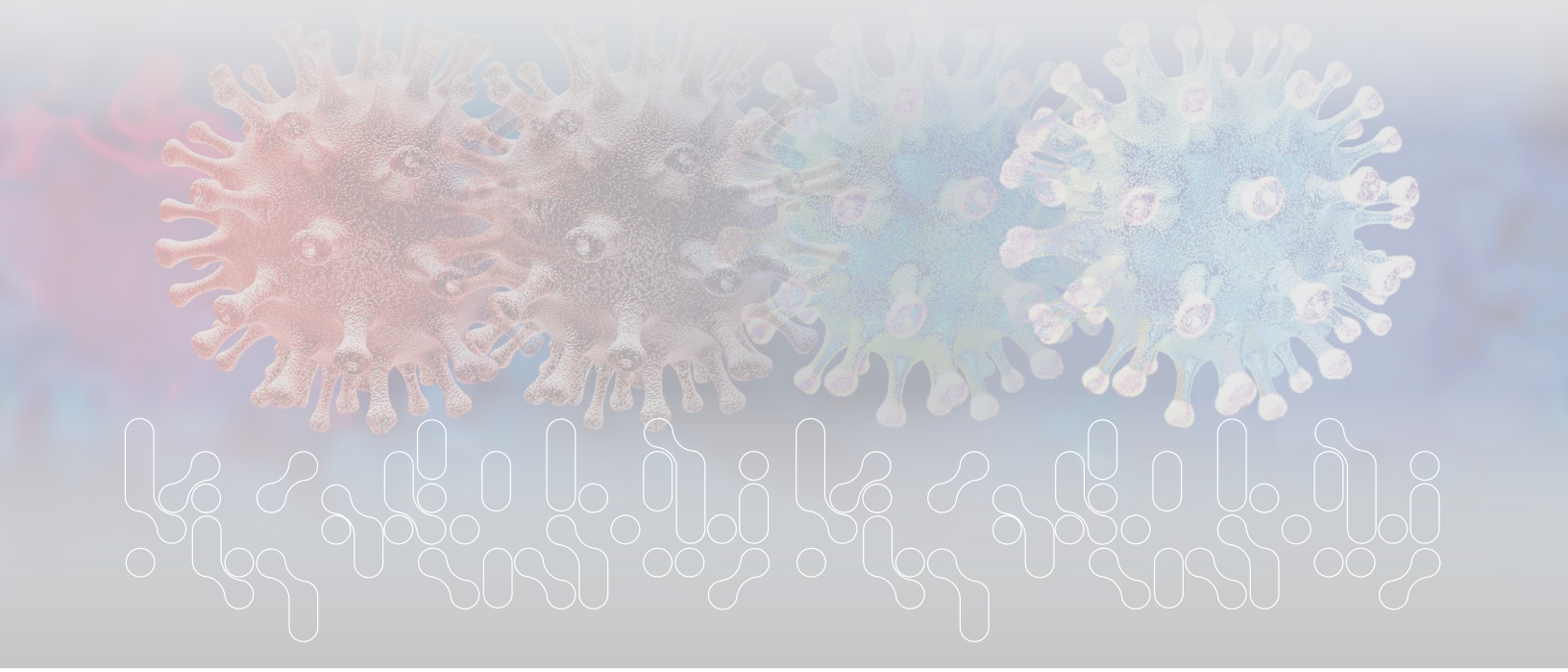


Reshaping the Future of Consumer Health through Decentralized and Digitally Enabled Strategies

Christopher Morris, BSc (Hons)
Senior Director, Consumer Health
Evidera, a PPD business

Mariah Baltezegar, MBA
Vice President and Head, Consumer Health & PPA Study Innovation
Real-World Evidence
Evidera, a PPD business

Background

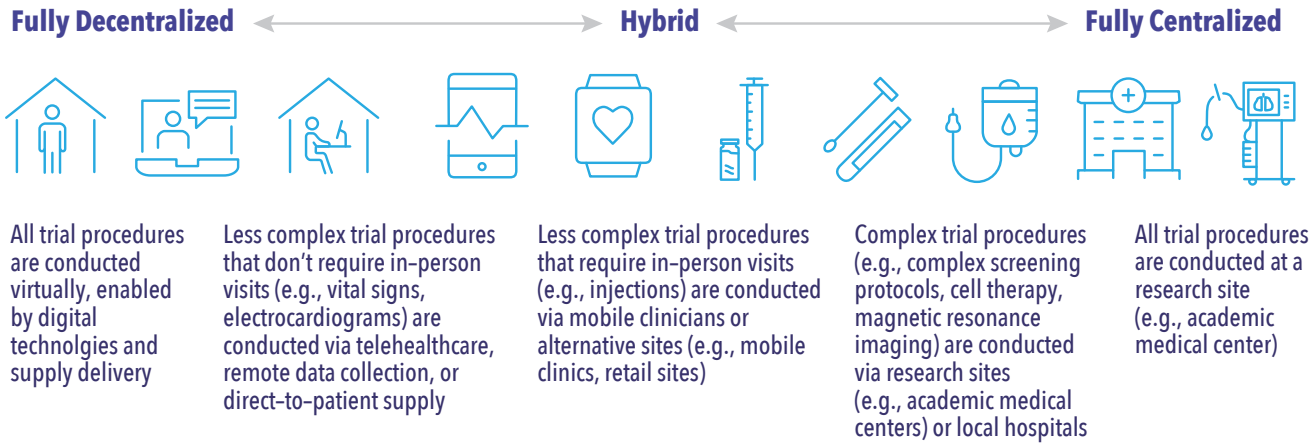
Consumers in 2021 are increasingly connected and the COVID-19 pandemic has only served to increase the need to stay connected. Consumers communicate, socialize, shop, and control their environment and health management using various technologies such as online apps, fitness wearables, and smart appliances all the time. They want services that make their lives simpler and more manageable. It is, in part, for this reason that clinical studies of consumer health products that are supported by digital and decentralized (DCT) technologies are attractive to participants. Since they are created to be consumer-centric, digital and DCT study technologies and services have created a spectrum of new clinical study models, ranging from digitally enabled studies to entirely DCT approaches, which effectively remove most of the labor-intensive inefficiencies of traditional studies.[1]

The use of computers, mobile devices, wearables, and other biosensors to gather and store huge amounts of health-related data has been rapidly accelerating. These data hold the potential to generate deeper health-related insights allowing us to better design and conduct


Christopher Morris


Mariah Baltezegar

Figure 1. Operational Approaches to Trial/Study Design



clinical studies to answer questions previously thought unanswerable. Additionally, with the development of sophisticated new data analysis platforms, researchers are better able to analyze these data and apply the results of that analysis to product development and approval.[2]

DCT research methods are not new to the consumer healthcare industry. Primary market research exploring new potential claims, such as the speed or duration of action of a product, or to evaluate the impact of new packaging or a new brand name has long been conducted utilizing online digital survey methods. However, more scientifically robust research in the consumer health space has been restricted by cost and time limitations driven by the marketing imperative to bring that claim to market rapidly.

Futureproofing Consumer Health Studies Using Today's DCT Strategies

Today, DCT elements mirror components of a clinical study that traditionally have been completed in a costly face-to-face setting. For example, eConsent and electronic questionnaires have been used in the pharmaceutical industry, replacing the need for paper forms, and enabling the collection of information directly from the patient — often in remote settings. By bringing these solutions into consumer health research, along with telehealth solutions that enable in-home video consultations, enhanced consumer involvement through instant messaging-style chat functions, and direct data collection from wearables, researchers can obtain a real-world view of a product with minimal inconvenience to the consumer.

Participation in clinical studies where consumers are asked to attend face-to-face clinic visits can become laborious for the consumer. Navigating the commute, wait times, physical assessments, and impact on day-to-day work and life commitments can negatively affect study retention resulting in missing or incomplete data and reducing the robustness of the data collected. DCT studies facilitate better engagement and retention due to the ability to create a near seamless fit with consumers' lifestyles.

Operational Approaches

Those diverse operational approaches shown in *Figure 1* allow for a broad spectrum of DCT and hybrid approaches. In the most complete form, a trial can be fully DCT, with enrollment and assessments taking place in a consumer's home, enabled by end-to-end digital tools and the self-administration of medicines. This model is gradually migrating from small early-phase and non-interventional/post-approval studies toward larger pivotal trials.[3]

While only a small percentage of clinical studies are fully DCT, many studies employ one or more DCT elements, such as ePROs and direct-to-patient supply, based on the suitability of the study population, endpoints, treatment modalities, etc., for these approaches. The industry is experiencing significant increase in uptake because of experience gained during the COVID-19 pandemic.[4] The use of electronic diaries and electronic patient-reported outcomes (ePROs) to support validated endpoints around pain and quality of life are now becoming normal practice in consumer health.

Traditional clinic visits will continue to be needed for complex procedures and specialized screening assessments such as magnetic resonance imaging. In this situation, hybrid trial designs allow other protocol touchpoints to be DCT or closer to the patients—for instance, through mobile clinics and primary-care physicians—whenever possible.

Enablers for DCT Designs in Consumer Health Research

Increased comfort with technology. Consumer uptake of digital technology is increasing year to year. Fitness wearables continue to show strong growth as do activities such as Peloton (workouts) and Strava (exercise tracking). Physicians' and sites' comfort with remote technologies has also increased because of the COVID-19 pandemic. Clinical-study investigators predict that a threefold increase in remote patient interactions will persist after the pandemic.[5]

Importance of convenience. Convenience is increasingly critical to patient enrollment and retention in clinical studies. Patients and physicians expect sponsors to consider patient convenience in trial designs, and investigators in many countries have predicted an increase in patient-centric trial features following the COVID-19 pandemic. This is particularly important in consumer health. Given much of the research is in non-life-threatening conditions, it is vital for successful enrollment that consumers are not inconvenienced outside of their normal day-to-day routine.

Maturing tools. Tools for remote data gathering such as mobile electronic clinical outcomes assessments (eCOA), novel sensors, actigraphy, camera, voice, and video are increasingly being validated, establishing standards for their broader use. Digital endpoints in consumer health such as cough frequency, sleep quality, stress levels, focus/attention, mobility, and cardiac fitness are being used more and more as primary endpoints.

Regulatory acceptance. Prompted by the COVID-19 pandemic, regulators have issued guidance permitting the use of alternative clinical trial approaches, such as remote monitoring, drug shipments to patient homes, home nursing, and alternative sites. Such advice will likely continue to evolve rapidly on a country-by-country basis. As we emerge from the pandemic it is anticipated that much of this guidance will remain and become a key enabler in consumer health research.

Partner ecosystem. The contract research organizations (CROs) that provide the backbone of clinical-trial services are investing in the emerging set of decentralization elements. Technology innovators are also investing and integrating point solutions to provide sponsors with more seamless and complete offerings.

Key Benefits of DCT Trials for Consumer Health

Today's crowded and highly competitive consumer health market makes meaningful product differentiation a challenge. Compelling claims, supported by scientific evidence, are vital to keep products and brands relevant in the minds of consumers, pharmacists, and other healthcare professionals.

Three key benefits in using DCT study strategies in consumer health research

1. Consumers could feel more engaged in the research and be more likely to adhere to study parameters and less likely to drop out when they feel they are not deviating too much from their normal day-to-day routines
2. Remote studies can help companies innovate the ways they collect evidence, with digital health tools enabling capture of new endpoints and opening new avenues for claims developments
3. When implemented correctly, DCT research can simplify execution, reducing the time for recruitment and enrollment and potentially reducing costs

In this whitepaper, we addressed how DCT and digital technologies can enhance the quality, speed, and relevance of data collection. It is time for the consumer health industry to think differently about claims development and embrace the new opportunities available through digital trials. To understand and realize the promise of these new strategies, companies should consider partnering with experts who can offer a strong history and track record of success in planning and executing DCTs, in addition to being experienced with and solely focused on the unique needs and challenges of the consumer health research landscape. ■

For more information, please contact info@evidera.com.

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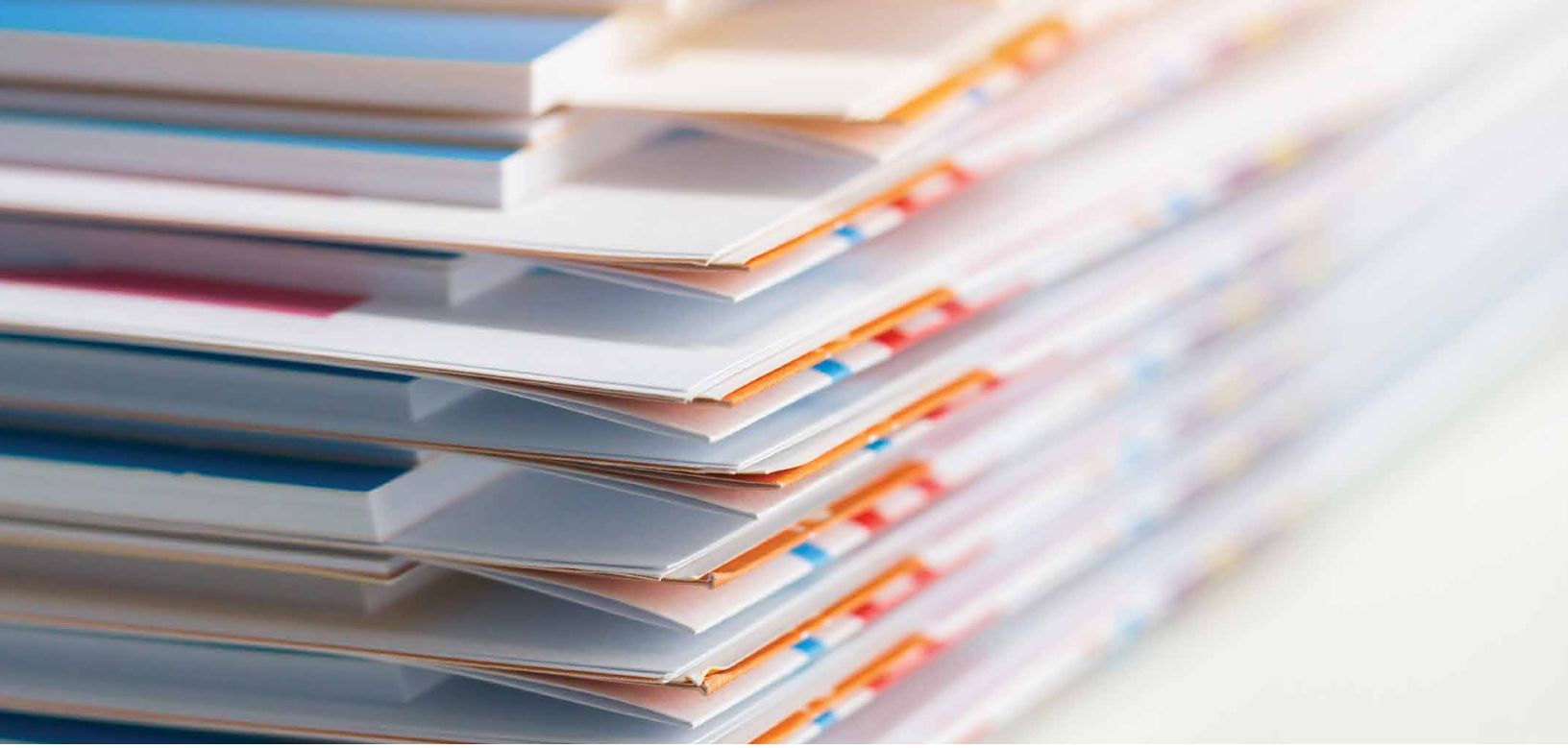


Mini-Global Value Dossiers (GVDs)
Smaller Can Be Better!

Donald Smith, PhD
Senior Scientific Director
Evidence Synthesis, Modeling & Communication
Evidera, a PPD business

Naomi Stapleton, BS
Associate Director
Evidence Synthesis, Modeling & Communication
Evidera, a PPD business

Leslee Masten, BA
Principal Market Access Writer
Evidence Synthesis, Modeling & Communication
Evidera, a PPD business

The use of streamlined, pharmaceutical product global value dossiers (called "mini-GVDs") has increased in the last two years. Mini-GVDs come in a variety of formats, can be useful in a number of different situations, and can be created prior to, near, or after product launch. This article will describe mini-GVDs, some of their potential uses, and also several benefits that they can provide to our clients and their affiliates.

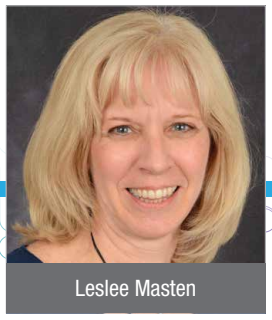
What is a Mini-GVD and What Does It Look Like?

A GVD is a document that contains information on a particular pharmaceutical product and the disease area/indication in which the product is used. The dossier also includes value messages that highlight the clinical, humanistic, and economic value of a product in a particular patient population. This document is used as a source of information by affiliates in the pharmaceutical and biotechnology industries to create reimbursement dossiers for local and regional submissions. GVDs help prepare these affiliates for discussions with public and private payers about their product and the value that it provides.

A standard full-length GVD covering disease burden, current treatments, unmet needs, and product value can


Donald Smith


Naomi Stapleton


Leslee Masten

often be 200 pages or more. In addition, traditional GVDs are often arranged by topic (e.g., epidemiology, economic value), rather than by value message, with the sections varying widely in terms of length and often exceeding 10 pages each.

In contrast, a mini-GVD is a streamlined document presenting typical GVD content in a more concise, digestible, navigable, and accessible format in approximately 50 pages. Furthermore, the content of a mini-GVD is typically organized by value message and color-coded by section for ease of use. The key supporting evidence for each value message in a mini-GVD is usually summarized in only one or two pages using a combination of text, tables, figures, and bulleted lists. Often, there is an emphasis on supporting visuals since these can be more engaging for the reader and help bring the product value story to life. *Figure 1* shows an example of one approach to developing a streamlined version of a mini-GVD.

In addition, a mini-GVD often contains a contents/index page that gives the reader an overview of the dossier, the value messages, and the supporting content. This index page frequently has hyperlinks so that the reader can easily navigate directly to any value message and/or supporting content that they wish. Appendices with tables and figures may also be included if there is a desire to include additional information on some of the most important studies. An example of an appendix table from a mini-GVD is shown in *Figure 2*.

Why Develop a Mini-GVD?

During the past couple years, there has been an increase in demand for GVDs that are comprehensive, but also streamlined. The more concise format of a mini-GVD provides some benefits over a traditional GVD. For example, the brevity of the mini-GVD allows the dossier to focus on the most important content, thus becoming less of a data repository and more of a story-telling tool. Our clients have found that this concise format is particularly useful for affiliates that do not require as much detail as a traditional GVD provides, including affiliates representing countries with less rigid health technology assessment (HTA) requirements, as well as affiliates that are responsible for multiple products in their region and have less time to review large dossiers for individual products.

Furthermore, the typical mini-GVD can be developed in 3 to 6 months in contrast to a standard GVD that usually takes 6 to 15 months to complete, which can be beneficial if development timelines are condensed. Another advantage of a mini-GVD is its flexible structure and format that can be adjusted to best meet the needs of the users based on the available data, the product strategy, and the needs of the client. Finally, a mini-GVD can be more cost effective than a traditional GVD due to its smaller size and shorter development timeframe.

When Should a Mini-GVD be Developed?

Standard full-length GVDs are typically developed as Phase III trial results start to become available, with the dossier content being finalized in time for product launch and

Figure 1. Example Mini-GVD Page*

3 Disease burden and unmet need

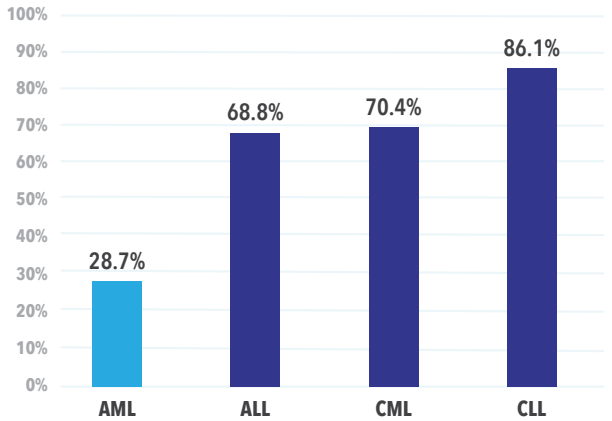
3.1 Disease burden

VALUE MESSAGE	*AML has the lowest survival rate of all leukemias and is associated with a dismal prognosis.*

AML is a cytogenetically and molecularly heterogeneous group of hematopoietic disorders that progresses rapidly and is frequently fatal without treatment.[1] A diagnosis of AML is associated with a dismal prognosis, and most adult patients with AML experience disease recurrence within 3 years of diagnosis or die from their disease shortly after diagnosis.[1]

Survival in patients with AML is lower than in patients with other leukemia.[2] In the US (2010 to 2016), the 5-year OS rate was lower in patients with AML (28.7%) than in patients with acute lymphoblastic leukemia (ALL; 68.8%), chronic myeloid leukemia (CML; 70.4%), and chronic lymphocytic leukemia (CLL; 86.1%) (Figure 1).[2] Another US study (2007 to 2013) showed that AML was associated with lower rates of 1-year OS among 75 to 84 year olds (18.2%) and ≥85 years olds (7.5%) than other hematological cancers, with the highest rates seen with CLL (91.8% and 81.6%, respectively).[3]

Figure 1. Five-year OS in the US (2010 to 2016)[2]



AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; OS = overall survival; US = United States

*Content is for example purposes only.
GVD = global value dossier

Figure 2. Example Appendix Table from a Mini-GVD*

Table 10. Summary of CAD incidence and prevalence data

Study design	Incidence	Prevalence
Countries: Norway, Italy (Lombardy region)		
Retrospective multicenter study of patients diagnosed with primary CAD conducted between June 2017 and January 2019 Excluded secondary CAD/CAS (clinically or radiologically overt lymphoma, other active cancer, or recent infection with Mycoplasma pneumoniae or Epstein Barr virus)	Italy: 0.048 per 100,000 per year Norway: 0.19 per 100,000 per year	Italy: 0.50 per 100,000 Norway: 2.05 per 100,000
Country: Denmark		
Registry study of patients diagnosed with CAD from 1977 to 2016	0.18 per 100,000 person-years	1.04 per 100,000 in 2015
Country: Denmark		
Registry study of CAD (identified by CAD-specific ICD-10 codes) in 2013	0.18 per 100,000 person-years	1.26 per 100,000 in 2013
Country: Norway		
Multicenter study of lab-confirmed primary CAD (based on new cases between 1995 and 2004)	0.10 per 100,000 per year	1.62 per 100,000
Country: France		
Single-center study of 83 patients with AIHA (1980 to 2000)	—	13% of patients with AIHA had CAD
Country: UK		
Single-center study of 865 cases of AIH (1961 to 1980)	Age ≥61 years: ~0.9 to 1.1 per 100,000 patients Age ≤50 years: ~0.1 to 0.2 per 100,000 patients	15% of patients with AIH had CAD

AIH = autoimmune hemolysis; AIHA = autoimmune hemolytic anemia; CAD = cold agglutinin disease; CAS = cold agglutinin syndrome; ICD-10 = International Classification of Diseases, Tenth Revision; UK = United Kingdom

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GVD = global value dossier

potentially updated as additional developments occur (e.g., new indications, availability of real-world data). Mini-GVDs offer flexibility in that they may be developed prior to, simultaneously with, instead of, soon after, or long after a full-length GVD.

Developing a Mini-GVD Prior to a Traditional GVD

Mini-GVDs can be developed before the Phase III, or even Phase II, trials of a product have commenced. A mini-GVD produced early in clinical development provides a good starting point for a full-length GVD and can also plant the seeds for the development of the corresponding value story. A mini-GVD that is developed early in the product lifecycle may be useful if:

- The users are unfamiliar with a particular disease area and/or the current treatment landscape
- A dossier would help address internal needs, but it is too early to start work on a full GVD to support a product launch
- There is an interest in defining the key evidence gaps and understanding how the available literature supports an early value story
- There are plans to use the product in multiple indications or disease populations and getting an early start on a dossier would facilitate other pre-launch activities

Mini-GVDs that are developed prior to a traditional GVD often contain fairly complete sections on disease burden and unmet need and well-supported value messages related to those topics. Depending on how early on in development the mini-GVD is generated, the disease burden and unmet need sections may be able to inform the design of Phase II and/or Phase III trials.

On the other hand, mini-GVDs that are developed prior to a full-length GVD may lack information related to product labeling, clinical trials, and/or economic models. Therefore, the sections on product information, clinical value, and economic value may be incomplete. However, these relatively brief sections can still be useful. For example, the clinical value section may contain information on the design of each main study along with a list of aspirational value messages related to the key endpoints.

Developing a Mini-GVD Simultaneously with a Traditional GVD

While developing a mini-GVD simultaneously with a traditional GVD is uncommon in our experience, it may appeal to those who feel that a mini-GVD might be a better companion piece to a full-length GVD than a GVD slide deck. Based on conversations with our partners and their operating companies, a mini-GVD may be preferable to a GVD slide deck in certain cases since a mini-GVD provides more information and detail than a GVD slide deck while still presenting the information of interest in a more visual and streamlined manner than a traditional GVD.

Developing a Mini-GVD Instead of a Traditional GVD

A mini-GVD may be preferred over a traditional GVD because it provides a fresh approach, giving affiliates the value story and key supporting evidence in a direct, impactful way. For example, a client expressed concern that its GVDs had been frequently growing in length and complexity, becoming more of a data repository than a compelling story-telling tool to facilitate market access. For their new product in development for a rare disease with no approved treatments, they wanted a streamlined GVD that presented the disease background, unmet need, and clinical evidence in a concise, digestible format. Our client also needed a way to ensure access to more detailed data and comprehensive reports when required by an affiliate. The mini-GVD for this product summarized the most important and compelling information in the body of the dossier, highlighting and illustrating key points with tables and figures. Links were provided to study details and additional data in the appendix. Instructions were provided so that external full reports and publications could be accessed for more in-depth information. Each section opened with key value message tables that included cross-references to supporting evidence either in the text or the appendix. The mini-GVD thus provided an easy to use resource for product value evidence to support global payer communications.

Developing a Mini-GVD Soon after a Traditional GVD

A mini-GVD may still be beneficial even if a traditional GVD has been developed recently. One example was a product whose GVD had recently been updated to reflect changes in current disease management, as well as to cover the product's multiple indications in different lines of therapy and age groups. The updated GVD had grown to a large size (nearly 300 pages) to accommodate descriptions of multiple pivotal trials and the competitive treatment landscape. Users of the GVD therefore had a potentially overwhelming amount of information available to them, and some affiliates found that the GVD was too long to read and too cumbersome to quickly find key information. While the increased level of detail in the full-length GVD was required for creating submission dossiers, a more concise presentation of the key information and overall narrative was also needed. The mini-GVD was developed as a resource that presented the evidence-based value story and key messages for the product in a clear, succinct, and accessible manner.

Tailoring the mini-GVD to the needs of the users and making it more digestible and navigable encouraged broad use of the dossier by the affiliates as a "go to" source for information. The more concise format was also positively received in its use as a companion to the full-length GVD for negotiations with payers in multiple countries.

In particular, the brevity of the dossier was found to be most useful in Latin American, Middle Eastern, and African markets, where HTA submissions may require less detail than European country submissions, or affiliates may be responsible for multiple products and have less time to review each GVD.

Developing a Mini-GVD Long after a Traditional GVD

Mini-GVDs can also be developed long after a full-length traditional GVD. One example where a mini-GVD proved beneficial involved a product that received initial approval in the US and EU approximately a decade ago. The next step in development was to prepare to support the launch of the product in several new countries and its re-launch in other countries. Since the original full-length GVD had not been updated since the initial approval of the product, there was a discussion with the client team about whether to update the existing GVD or generate a completely new one. Since there was also a desire to update the evidence base to include a series of publications about recent real-world evidence that supported the clinical, humanistic, and economic value of the product as a treatment of choice in the disease area, we suggested developing a clear and concise mini-GVD that could highlight the latest data, the current value narrative, and be more easily accessible to the affiliates.

Conclusions

As mentioned earlier, the use of mini-GVDs has been on the rise in recent years, and there are a variety of reasons for their increasing use. Many companies have found that mini-GVDs are useful as either a companion piece to a full-length GVD or as a stand-alone piece that provides all of the pertinent information in a streamlined and accessible format. Their popularity is also affected by the ability to develop them prior to, simultaneously with, instead of, soon after, or long after a full-length traditional GVD. The adaptable format of mini-GVDs means that they can be designed for the unique needs of the users and the specific characteristics of the product, allowing companies flexibility in creating the right communication vehicle for the right audience at the right time. In addition, they can be developed more quickly than standard GVDs and at a lower cost, which may be a more attractive option in certain situations. As competition increases and time becomes even more critical in getting products to market, mini-GVDs are one growing option providing companies the ability to plan and execute their evidence strategies and dissemination plans in the most effective way possible. ■

For more information, please contact info@evidera.com.

Evidera's Presentations at **ISPOR 2021 Europe Virtual**

WORKSHOP

FRI., 3 DEC.; 12:30 – 13:30

Use of Whole Disease Models and Pathway Models in Health Economic Research: Benefits and Risks

Clarke PM, **Caro JJ**, Jin L, Tappenden P

ISPOR FORUMS

TUE., 30 NOV.; 12:30 – 13:30

When and How Can Health-Preference Measures Be Transferred Between Contexts?

Marsh K, Johnson FR, **Krucien N**, Roudijk B

THUR., 2 DEC.; 16:00 – 17:00

ISPOR Task Force on Emerging Good Practice in Quantitative Benefit-Risk Assessment - A Roadmap

Tervonen T, Ho M, Pignatti F, Veldwijk J

ISSUE PANEL

THUR., 2 DEC.; 11:00 – 12:00

How and When Should Evidence from Patient Preference Studies be Integrated into HTA: Aligning Methodological, Agency and Industry Perspectives

Marsh K, Cleemput I, Danyliv A, de Bekker-Grob E

PODIUM PRESENTATIONS

P18: Patient Preferences for Attributes of a MULTI-Cancer EARLY Detection Test: A Discrete Choice Experiment (DCE) Quantitative Pilot Study

Gelhorn H, **Ross M**, Kansal A, Fung E, Seiden M Chung KC

P37: The Cure Myth: Experience from Recent Health Technology Assessment (HTA) Submissions in Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL)

Mohseninejad L, **Hardy A**, **Westley T**, **Kongnakorn T**

POSTERS

POSA101: Modeling Approaches in Cost-Effectiveness Analyses of Cell Therapies for Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Hernandez LG, **Martin A**, Brouwer ES, Chun D, Cheng LI, Bernhardt A

POSA126: An Economic Analysis of Empagliflozin versus Sacubitril/Valsartan in Patients with Heart Failure with Reduced Ejection Fraction (HFrEF) in the United Kingdom (UK)

Reifsnider O, **Tafazzoli A**, Bellanca L, **Litkiewicz M**, **Stargardter M**, Linden S

POSA128: Cost-Effectiveness Analysis of Avelumab Plus Best Supportive Care (BSC) vs BSC Alone as a First-Line (1L) Maintenance Treatment for Patients with Locally Advanced or Metastatic Urothelial Carcinoma in Taiwan

Chang W, **Xiao Y**, Lin A, Su P-J, Goh C, Wu E, Liu K, Chou P, Kuo K, Palencia R, Chang J, Kearney M, **Kapetanakis V**, **Benedict A**

POSA147: A Review of Methods Used to Estimate Pediatric Utility Values in Health Technology Appraisals across Different Agencies

Purushotham S, **Brown L**, **Francmanis E**, **Browne C**, **Agbeleye O**, **Forbes C**, **Bungey G**

POSA210: Decentralized Study Methods: A Summary of the Regulatory Landscape in the Sars-COV-2 Era and Beyond

Bevan A, **Baltezegar M**

POSA248: Consistency of Metastatic Non-Small Cell Lung Cancer and Renal Cell Carcinoma Treatment Patterns Across Italian Regions

Rivolo S, **Emeanuru K**, **Capart P**, **Benedict A**

POSA254: An Initial Framework to Describe and Classify Integrated Scientific Advice Procedures for Vaccines

Olid Gonzalez A, **Schmidt M**, **Bending M**

POSA260: Common Drivers in Countries That Are Developing HTA Systems Have Led to Similar Challenges for Innovative Therapies

Goto D, Spiteri C, **Griffiths J**, Iliadi Alexiou A, **Parkinson M**

POSA262: The Use of Akaike Information Criterion and Bayesian Information Criterion Rules of Thumb in NICE Oncology Appraisals - a Targeted Review

Bungey G, **Brown L**, **De Boisvilliers S**, **Teloian D**, **Hardy A**, **Guerrero-Ludena R**, **Peter B**, **Xiao Y**, **Benedict A**

POSA274: Uncertainty Around Utility Decrements Due to Progression in Economic Models: The Case of Multiple Myeloma (MM)

Mohseninejad L, **Kovacs V**, **Chapman R**

POSA288: Virtual Reality and Gaming Technology in Clinical Research: Past Trends and Future Prospects

Bevan A, **Baltezegar M**, **Saragoussi D**

POSA308: A Comparison of STC and MAIC Under Misspecification of the Treatment Effect and Effect-Modifier Relationship

Ishak KJ, **Kapetanakis V**, **Proskorovsky I**, **Fahrbach K**

POSA315: A Computationally Efficient Alternative Method for Probabilistic One-Way Sensitivity Analysis

Gal P, **Benedict A**

POSA321: Estimating Correlations between Relative Efficacy of Immuno-Oncology Monotherapies across FOUR Oncology Indications

Freitag A, **Ract M**, **Altaf-Haroon I**, **Dodman S**, **Kapetanakis V**

POSB23: Tafasitamab PLUS Lenalidomide vs SOC Including 3 Rituximab-Based Treatments or Lenalidomide Monotherapy in Patients with NON-Transplant Eligible Relapsed or Refractory Diffuse Large B-Cell Lymphoma - a Matching Adjusted Indirect Treatment Comparison

Cordoba R, **Prawitz T**, **Westley T**, **Sharma A**, **Kapetanakis V**, Sabatelli L

POSB44: Drivers of Value-Based Price (VBP) for a Multi-Cancer Early Detection (MCED) Test

Tafazzoli A, Ramsey SD, **Shaul A**, **Chavan A**, **Ye W**, Chung KC, Kansal AR, Fendrick AM

POSB115: Approaches for Modeling Treatment Effect Waning in Markov Cohort Models in NICE Reviews of Non-Oncology Agents

Stargardter M, **Sachdev R**, **Milev S**

POSB289: Emergence of Applications for Digital Health Technologies and Details of HTA Assessments for Digital Health in Europe

Sidhu C, Ohanwusi E, **Bending M**, **Sullivan N**

POSB315: ASM Revisited: Simplifying the Backward Shift

Ishak KJ, **Prawitz T**, **Kapetanakis V**

POSB372: Patients' Preferences for Connected Insulin Pens: A Discrete Choice Experiment Among Diabetes Patients in the UK and US

Heidenreich S, **Seo J**, **Aldalooj E**, Poon JL, Spaepen E, Eby EL, Newson RS

POSB378: Health State Utilities Associated with Hyperphagia

Howell TA, **Matza L**, Mallya UG, Goldstone AP, Butsch WS, Lazarus E

POSC4: Modeling Health-Related Outcomes with Avelumab as a First-Line Maintenance Treatment Following Chemotherapy vs Best Supportive Care (BSC) for Patients with Locally Advanced or Metastatic Urothelial Cancer in the UK

Critchlow S, **Xiao Y**, Crabb S, Eccleston A, Christoforou K, Amin A, Bullement A, Deighton K, Chang J Kearney M, **Kapetanakis V**, **Benedict A**

POSC118: Cost-Effectiveness of Abrocitinib for the Treatment of Patients with Moderate-to-Severe Atopic Dermatitis in Canada

Stargardter M, DiBonaventura M, **Milev S**, On PV, Cappelleri JC, **Sardesai A**, Galos C, Hong HC

POSC143: Comparison of Model Structures used in NICE and ICER Cost-Effectiveness Evaluation

Milev S, **Sardesai A**, **Sunil Raj S**, **Taylor A**, **Sala J**, **Zou D**

POSC256: Application of Progression-Free Survival as Surrogate Endpoint for Overall Survival in NICE Reviews of Advanced Breast Cancer Drugs

Zou D, **Sun A**, **Musci R**, **Milev S**

POSC328: Impact of Treatment Schedule on Adherence and Persistence in Osteoporosis Patients Receiving Long-acting Therapeutics

Martin A, **Fahrbach K**, **Forbes C**, Rosado Cristino J, Electricwala B

POSC360: The Patient Perspective on Achieving Near Normoglycemia in People with Type 2 Diabetes

Gelhorn HL, **Ross MM**, Shinde S, Thieu VT, Boye KS

Upcoming Presentations

ACAAI 2021

November 4-8, 2021 | New Orleans, LA, USA

ePOSTERS

Dysphagia Days as a Clinical Marker of EoE Treatment Response

Hirano I, Rothenberg ME, Zhang S, Rodriguez C, Charriez C, **Coyne K**, Dellon ES

Asthma Impairment and Risk Questionnaire (AIRQ) at Baseline Predicts 12-Month Health-Related Quality of Life (HRQoL)

Murphy KR, Chipps B, Wise RA, Beuther DA, George M, McCann W, Zeiger RS, Gilbert I, Eudicone JM, Gandhi HN, **Harding G**, **Ross M**, Reibman J

AIPO 2021

November 6-8, 2021 | Milano, Italy

ABSTRACT ONLY

Healthcare Resource Use & Costs of Pertussis in Adults with Asthma: A Retrospective Study in England

Bhavsar A, Aris E, Harrington L, Simeone JC, Ramond A, **Lambrelli D**, Papi A, Meszaro K, Jamet N, Sergerie Y, Mukherjee P

AONN+ Annual Conference

November 17-21, 2021 | VIRTUAL CONFERENCE

POSTER

Evaluating the User-Perceived Benefit of a Virtual Patient Education and Support Community: LVNG With Lung Cancer

Sandy B, **Martin ML**, Bucklen K, Hall L, Wonser D, de Renne G

AES 2021 Annual Meeting

December 3-7, 2021 | Chicago, IL, USA

POSTERS

Patient Profiles in Drug Resistant Epilepsy (DRE): Vagus Nerve Stimulation (VNS) vs. Responsive Neurostimulation (RNS)/Deep Brain Stimulation (DBS)

Halhol S, Vincent T, Li Q, Stokes ME, Berger A, Lam S, Danielson V, Barion F, Murphy J, Lassagne R, Hagen E

The Patient Journey Prior to Neurostimulation in Drug-resistant Epilepsy (DRE)

Halhol S, Vincent T, Li Q, Stokes ME, Berger A, Lam S, Danielson V, Barion F, Murphy J, Lassagne R, Hagen E

ASH Annual Meeting of the American Society of Hematology

December 11-14, 2021 | Atlanta, GA, USA

POSTER

Considerations for Optimal Administration of Chimeric Antigen Receptor (CAR) T-Cell Therapy Programs: A Multi-Stakeholder Qualitative Analysis

Hoda D, Faber EA, Deol A, Hunter B, Crivera C, Riccobono C, Garrett A, Jackson CC, Fowler J, **Berger A, Lorden AL, Stewart R**

Recent Presentations

AMCP Nexus 2021

October 18-21, 2021 | Denver, CO, USA

POSTER

Patient Perspectives on Implementation of a Long-Acting Injectable Antiretroviral Therapy Regimen in HIV US Healthcare Settings: Final Month 12 Results from the CUSTOMIZE Study

Flamm J, Garris C, D'Amico R, Dalessandro M, McHorney CA, Mansukhani SG, Benson P, Thedinger B, Salazar D, Tanda N, Fricker J, Czarnogorski M

SASP 2021 Conference

October 7-8, 2021 | VIRTUAL CONFERENCE

ORAL PRESENTATION

Pharmacy Dispensing Records for Topical Diclofenac in Sweden, a Retrospective Analysis of Real-World Data

Rampartaap V, Csoke E, Nair D, **Wilcox T**, Norrefalk JR, Sethi V, Shanga G, Fabrikant K

ESMO 2021

September 16-21, 2021 | VIRTUAL CONFERENCE

POSTER

Health-Related Quality of Life (HRQoL) in the ASCENT Study of Sacituzumab Govitecan (SG) in Metastatic Triple-Negative Breast Cancer (mTNBC)

Loibl S, Loirat D, Tolaney S, Punie K, Oliveira M, Rugo H, Bardia A, Hurvitz S, Brufsky A, Kalinsky K, Cortes J, O'Shaughnessy J, Dieras V, Carey L, Gianni L, Gharaibeh M, Moore L, **Shi L**, Piccart M

ESC 2021

August 27-30, 2021 | VIRTUAL CONFERENCE

POSTER

Key Aspects of Statin Intolerance Leading to Treatment Discontinuation: A Patient Perspective

Catapano AL, Wiklund O, **Bushnell DM, Martin ML**, Sidelnikov E, Vrablik M

WCO-IOF-ESCEO London 2021

August 26-29, 2021 | VIRTUAL CONFERENCE

POSTERS

Pharmacy Dispensing Records for Topical Diclofenac and Concomitant Medicines in Germany, a Retrospective Analysis of Real-World Data

Deutsch D, Fabrikant K, Sethi V, Shanga G, Rampartaap V, **Wilcox T**, Csoke E

Pharmacy Dispensing Records for Topical Diclofenac in Sweden, a Retrospective Analysis of Real-World Data

Rampartaap V, Csoke E, Nair D, **Wilcox T**, Norrefalk JR, Sethi V, Shanga G, Fabrikant K

ICPE 2021

August 23-25, 2021 | VIRTUAL CONFERENCE

POSTERS

Improving Accuracy for Prospective Pregnancy Registry Enrollment Targets

Veley K, Covington D, Pozin P, Buus R, Okala S

Methodologic Challenges and Considerations for the Collection of Dietary Intake Data in Real-World Populations

Brett NR, Bassel M, Hong M, Margolis MK

IAS 2021

July 18-21, 2021 | VIRTUAL CONFERENCE

ePOSTER

CAB+RPV LA implementation Outcomes and Acceptability of Monthly Clinic Visits Improved During COVID-19 Pandemic Across US Healthcare Clinics (CUSTOMIZE: Hybrid III Implementation-Effectiveness Study)

Czarnogorski M, Garris C, **Stassek L**, Mansukhani S, D'Amico R, Dalessandro M, Williams W, Wu S, Wohlfeiler M, Flamm J, Benson P, Zurawski C, Bosse M

ORAL PRESENTATION

CUSTOMIZE: Overall Results from a Hybrid III Implementation-Effectiveness Study Examining Implementation of Cabotegravir and Rilpivirine Long-Acting Injectable for HIV Treatment in US Healthcare Settings; Final Patient and Provider Data

Czarnogorski M, Garris C, D'Amico R, Flamm J, Sinclair G, Wohlfeiler M, Mena L, Dalessandro M, McHorney C, Mansukhani S, Williams W, Merrill D, Spreen W

ECCO 2021

July 2-3 & July 8-10, 2021 | VIRTUAL CONFERENCE

ePOSTER

Optimising Vedolizumab in Treatment Sequences for Crohn's Disease: Results from a Simulation Model Using Real-World Evidence

Louis E, **Nikolaou A, Litkiewwicz M**, Agboton C, Wang S, Armuzzi A

DIA 2021

June 27-July 1, 2021 | VIRTUAL CONFERENCE

ePOSTER

A COVID-19 Epidemiologic Model to Enhance Efficiency Through Evidence-Based Site Selection for Vaccine & Treatment Trials

Caro JJ, Schaumberg D

SHORT COURSE

Best Practices for Business Communications: How to Communicate with Maximum Impact

Chen D

SESSION SPEAKER

Creating Efficiencies for Long Term Follow Up (LTFU) Studies

Rich T, Baltezegar M

McGill University Pharmacoepidemiology Courses Summer Session 2021

June 14-18, 2021 | VIRTUAL

SHORT COURSE

EPIB 654 - Pharmacoeconomics for Health Technology Assessment

Caro JJ

EHA 2021 Virtual

June 9-17, 2021 | VIRTUAL CONFERENCE

ABSTRACT ONLY

Validation of Algorithms to Identify First-Line Therapy (Induction and Maintenance) for Multiple Myeloma for Use in Electronic Healthcare Databases

Berger A, Ailawadhi S, **Shah S, Fraeman K, Saragoussi D, Buus R, Nguyen B**, Cherepanov D, Romanus D

ASCO 2021 Annual Meeting

June 4-8, 2021 | VIRTUAL CONFERENCE

ABSTRACT ONLY

Evaluating the User-Perceived Benefit of a Virtual Lung Cancer Patient Education and Support Community: LVNG With Lung Cancer

Martin ML, Bucklen K, Hall L, Sandy B, Wonser D, de Renne G

JSN 2021

May 19-22, 2021 | Kyoto, Japan

ORAL PRESENTATION

Japanese Clinical Trial Participants' Experiences of Migraine and Erenumab Treatment

Hasebe M, Takashima T, Igarashi H, **Duenas A, Dias-Barbosa C**, Chandler D, Yoshida R, Numachi Y, Adachi K, **Hareendran A**

ATS 2021

May 14-19, 2021 | VIRTUAL CONFERENCE

EPOSTER

Systematic Review of Real-World Effectiveness and Safety Studies of Mepolizumab in Treating Severe Eosinophilic Asthma

Israel E, Canonica GW, Brusselle G, Yang S, Howarth P, **Martin A**, Koufopoulou M, Smith SG, Alfonso-Cristancho R

Recent Publications

Abbott M, McKenzie L, Guizar Moran BV, **Heidenreich S**, Hernández R, Hocking-Mennie L, Clark C, Gomes J, Lampe A, Baty D, McGowan R, Miedzybrodzka Z, Ryan M. Continuing the Sequence? Towards an Economic Evaluation of Whole Genome Sequencing for the Diagnosis of Rare Diseases in Scotland. *J Community Genet.* 2021 Aug 20. doi: 10.1007/s12687-021-00541-4. Online ahead of print.

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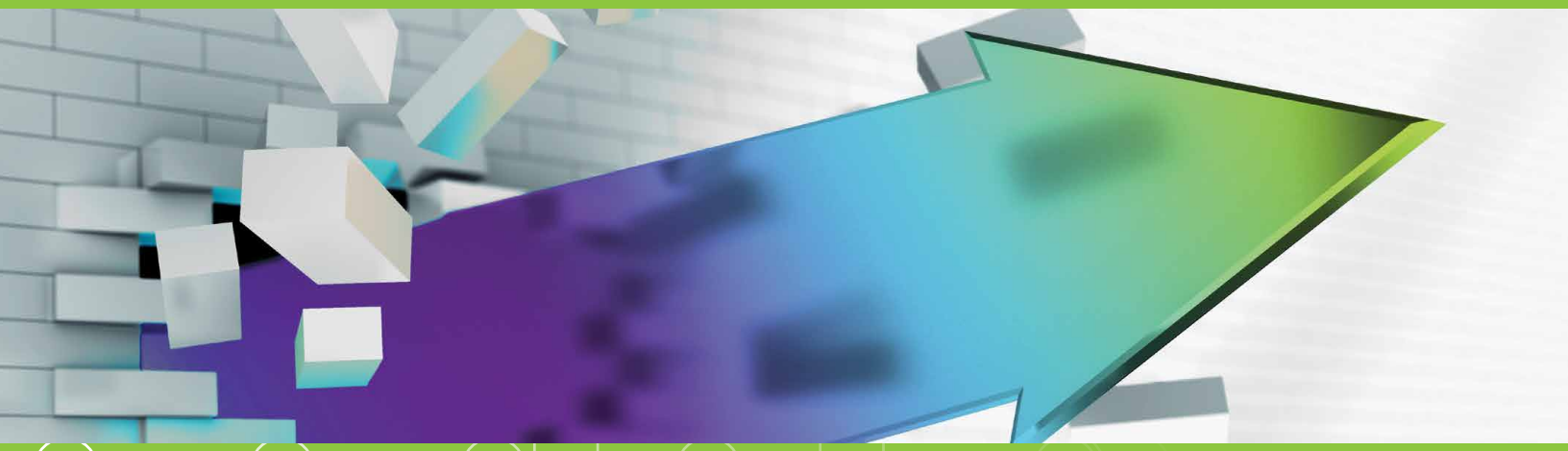

CORPORATE HEADQUARTERS
7101 Wisconsin Avenue, Suite 1400
Bethesda, MD 20814

contact: Susan Potter Couch
email: info@evidera.com

evidera.com

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