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From cause to care: Triple surveillance for better outcomes in birth defects and rare diseases

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ABSTRACT

Better outcomes are a priority for all those who care about birth defects and rare diseases. Public health surveillance and epidemiologic data tracking historically have provided good data on disease occurrence but at most uncertain value in promoting better outcomes, be these in terms of supporting primary prevention or better care.

We propose three enhancements to improve the value of surveillance. First, merge: eliminate the largely artificial separation between birth defects and rare diseases in surveillance. Second, expand the scope of surveillance to 'triple surveillance': include in surveillance the three components of the causal chain from primary cause (e.g., folic acid insufficiency) to disease occurrence (e.g., spina bifida prevalence) and further to health outcomes (e.g., mortality, morbidity). Third, integrate public health with clinical surveillance: streamline data collection (avoid 'recreational data collection') and use the data rapidly not only for epidemiologic assessment but also for evaluation and improvement of clinical care.

Many countries have one or more of the elements of this framework already in place. Typically, however, they are not integrated, and work and data get wasted. Fundamentally, these enhancements require rethinking priorities, partnerships and data sharing policies. By reducing waste (e.g., activities leading to data being collected but not used) they will add value and probably decrease costs. Importantly, such systems can help make visible the health issues of a population and the benefits (or lack thereof) of interventions, and support quality improvement in prevention and delivery of care.

1. Introduction: two groups of conditions for surveillance to improve outcomes

In recent years, congenital anomalies and rare diseases have increased in relevance and visibility not only in clinical practice and public health, but also in policy and social media. More countries are undergoing the 'epidemiologic transition' from high infant mortality driven by infectious diseases and preventable conditions of the newborn, to lower infant mortality resulting from complications of prematurity and congenital anomalies. Families and patients are taking to new forms of communication to influence care and policy related to rare diseases, most of which are genetic and many are symptomatic before adulthood.

With this still evolving but clear situation, an important question is what can be done to promote improvements in outcomes – better primary prevention where possible, and otherwise better treatments and optimal health outcomes.

Clearly these improvements are primarily driven by direct clinical interventions and effective public health policies: examples include folic acid fortification to prevent neural tube defects, diabetes screening and treatment to improve diabetes-associated pregnancy outcomes (congenital anomalies, complications of the newborn, etc.), and newborn screening to improve outcomes in children with metabolic disorders and congenital heart disease. Indirectly, but importantly, clinical and public health surveillance have a major role in ensuring that these preventive and therapeutic interventions can reach their full potential – that fortification indeed reaches all population groups, that diabetes screening programs are not creating or deepening health disparities, and that newborn screening continue to provide a positive ratio of benefits over costs and risks.

The issue addressed here is whether surveillance can truly help improve outcomes in rare diseases and congenital anomalies. The answer that we wish to propose is a qualified 'yes, if … '. The two main conditions discussed here are a) if surveillance abolishes the largely artificial distinction between congenital anomalies and (most) rare diseases, by embracing both in its activities; and b) if surveillance

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restructures from being an activity solely focused on tracking the occurrence of disease (e.g., prevalence and trends) and expands into 'triple surveillance' (Botto and Mastroiacovo, 2018)– tracking the causal chain from disease cause to disease occurrence and further to disease outcomes and using these data not only for epidemiologic assessment but also to improve clinical care.

Such model of surveillance, we argue, could help improve outcomes both on a personal and a population level. Elements of this model are beginning to be implemented in some areas, but not yet frequently, systematically, or fully, so that the value of such model of triple, comprehensive surveillance has not been proven in practice. Nevertheless, we present a few examples of high value opportunities that could be rapidly implemented in practice, and which could decrease the marginal cost of surveillance as is currently implemented and increase its effectiveness for clinicians, researchers, and families.

2. Merging the surveillance of rare diseases and congenital anomalies: value and rationale

Registries and surveillance of congenital anomalies have a long history, spanning decades and reaching back in many cases to the reaction to the thalidomide tragedy. After the birth of many children with devastating limb anomalies following the ingestion of (at the time) a seemingly safe medication, several countries implemented some form of surveillance of congenital anomalies with the stated goal of providing the population with a 'safety net', i.e., an ongoing system to detect and control such events as early and quickly as possible. Whereas what is encompassed under the rubric of (major) congenital anomaly varies in different systems, the general definition can be simplified as a congenital condition of prenatal origin that impacts on health and quality of life and requires treatment. The WHO definition is somewhat more inclusive, in that it includes functional as well as structural conditions (e.g., metabolic disorders in addition to congenital malformations).

Rare disorders, on the other hand, are defined not by their nature but by their number – conditions whose occurrence (or population prevalence) is below a somewhat arbitrary threshold – In the United States, fewer than 200,000 people, or in Europe, 1 in 2000 people or fewer. As a group, however, rare diseases affect many people: an estimated 30 million in the Europe, and approximately the same in the United States.

Not all rare diseases are genetic or congenital (some are infections or rare cancers, for example), but many are, and include also congenital anomalies and syndromes with congenital anomalies.

However, from the point of view of many families, clinicians, and health care systems, the distinction between rare pediatric diseases and congenital anomalies is blurred and artificial. From a clinician's and health system perspective, for example, many conditions, from spina bifida detected at birth or prenatally, to PRPS1 deficiency detected at age 12 years (CMTX5 OMIM 311070) in an undiagnosed and rare disease program (Table 1), are seen in related settings, raise similar diagnostic questions, may be incorporated in newborn screening, and require substantive team-based interventions in the hospital and close follow-up by the pediatrician at home. These examples (Table 1) are not imagined, and they have all been seen by one of the authors (LDB) as part of his specialty clinics or inpatient service.

From the perspective of the family, rare diseases and congenital anomalies raise similar fundamental questions (Table 2), from understanding the nature of the condition, the treatment, and the implications for the child and (because most have a genetic basis) for the rest of the family. Thus, from the point of view of what the family wants and what the health care system can and should provide – better diagnosis, care/cure, and outcomes – the line between congenital anomalies and many pediatric rare diseases is blurry and unhelpful.

Historically however, programs addressing congenital anomalies and rare diseases have tended to have a different evolution, at times different priorities, often different strengths as well as gaps (Table 3).

Table 1
Commonalities between rare disease and congenital anomalies: presentation, diagnosis, evaluation, and management.

Setting	Home	Newborn nursery	Skeletal dysplasia clinic	Metabolic clinic	Genetics/Undiagnosed Disease program
Clinical vignette	Newborn girl born at home, midwife notices clubfoot and open lesion on lower back	Newborn girl, term, APGARs 8 and 8. At 11:00 pm nurse noticed rapid breathing and ashen color	Newborn boy, healthy looking, term, length 48 cm, OFC 37.5cm. Pediatrician sends to clinic after 1-week exam	6-month girl, to bed with fever, not eating. Mother finds her at midnight unresponsive	12-year old boy, since age 5 loosing vision, hearing, walking. 7 yr diagnostic odyssey
Condition	Lumbar spina bifida	Tetralogy of Fallot	Achondroplasia	MCAD deficiency	CMTX5
Frequency (approx.)	1 in 1000 (or less in countries with effective fortification)	1 in 2000	1 in 25 000	1 in 15 000	Very rare
Genetics	Not Mendelian: majority related to folic acid insufficiency	15% due to del 22q11, sporadic or familial	FGFR3 G380R mutation Autosomal dominant	ACADM autosomal recessive, common 985 A > G mutation	PRPS1 deficiency, X-linked recessive, leading to decreased purine pool
Time of diagnosis	Birth	Birth to weeks	Birth to weeks	Birth to years	Years
Diagnostic method	Clinical exam	Echocardiogram	Radiographs	Plasma acylcarnitine profile	Whole exome sequencing
Newborn screening	Clinical exam	Pulse oximetry	No (> 20 weeks gestational age)	Yes (by Tandem MS)	No
Management	Surgery, specialty team-based care; primary prevention (recurrence, occurrence)	Surgery, medical follow up	Health guidelines, trials	Fasting precautions, emergency protocol	Trial treatment with purine replenishing supplements (e.g., SAM)

Note: OFC, occipito-frontal circumference; MCAD deficiency, Medium-chain acyl-CoA dehydrogenase deficiency; CMTX5, Charcot-Marie-Tooth X linked type 5; tandem MS, tandem mass spectrometry; SAM, S-adenosylmethionine.

Table 2
Key questions of the family when confronted with a congenital anomaly or a rare pediatric disease.

Question	Key theme	Comment/Example
What is this?	Diagnosis	Typically the first question. Best assessed by expert pediatrician or clinical geneticist. Can be easy (e.g., spina bifida at birth) or more difficult (e.g. rare Mendelian disorder with expanded phenotype, requiring whole exome sequencing for diagnosis)
What will happen now?	Outcomes	Typically the next question after the diagnosis, together with the next question. Can be particularly difficult to answer for rare or new disorders because of the scarcity of data. Surveillance programs and disease registries can help considerably.
How can we best treat it?	Care (Cure)	Care is always possible, even if a true cure is rarely available currently. Congenital anomalies can be completely fixed (e.g., cleft lip) or treated (e.g., complex cardiac anomalies). For certain metabolic conditions (e.g., MCAD deficiency), treatment (e.g., adherence to fasting precautions) can be similar to a cure in terms of outcomes (e.g., prevention of morbidity and mortality). For several conditions (e.g., achondroplasia), management focuses on anticipating complications (using established guidelines) while clinical trials assess pathway-based treatments.
Why did it happen?	Cause	May not be an explicit question from families at first, but should be elicited in counseling because of common feelings of guilt on the part of parents. The cause can often (but not always) be the product of the diagnostic process, in which case it can also provide reassurance (e.g., in the case of a *de novo* mutation), a more precise assessment of risk (see next question), or the possibility of preventing reoccurrence (e.g., enhanced folic acid protocol in case of spina bifida)
What will happen to my family?	Risk	Eventually many families with ask this question, possibly in follow up visit, after the immediate necessities of the child are taken care of. A precise answer typically depends on the ability to identify the genetic cause (e.g., gene mutation) or infer it (e.g., MCAD deficiency biochemically confirmed), or the environmental risk factors (e.g., maternal diabetes or folic acid insufficiency for some congenital anomalies)

For example, the epidemiology of congenital anomalies is typically better known even for rare congenital anomalies than for many rare diseases, due in large part to the long-standing surveillance programs in many areas and countries. Rare disease programs, on the other hand, tend to focus on care, cure, and family support, and have strong advocates in the public space. For example, the 2020 objectives of the International Rare Disease Research Consortium (IRDIRC) includes delivering 200 new therapies and delivering means to diagnose most rare diseases; the National Organization for Rare Disorders (NORD) has in its mission statement a similar focus on diagnosing, treating, and curing rare disorders. Rare disease programs are also more commonly supported by research and industry and centered in academic institutions, whereas congenital anomaly programs are historically an activity of public health departments with some but typically limited direct clinician involvement. Looking forward, however, it is helpful to note how the strengths of one program can be applied to the other program and vice versa (Table 3), if these programs collaborate, share, or merge. For example, the epidemiologic experience and expertise of congenital anomaly programs can help support the systematic and much needed assessment of prevalence, morbidity, and mortality in many rare diseases, using methods that take into account potential biases and referral patterns that rare disease registries might have. Conversely, the extensive experience of many rare disease registries in systematically assessing outcomes and the powerful examples of advocacy of rare disease communities can serve well the development of stronger congenital anomaly programs. Ideally, in fact, a shared program would assess and track both groups of conditions, with added value in terms of quality and timeliness of data generation, analysis, and use, and probably also in terms of public support.

Given these functional and systemic commonalities between many congenital anomalies and rare disorders, it seems reasonable to include them within a system of pediatric surveillance, ideally from the prenatal period if possible, and over time. However, if such surveillance is to provide significant value for all stakeholders – families, clinicians, researchers, health care system – it is worth reflecting on what surveillance typically offers now and what it might offer instead if restructured according to these stakeholders' common priorities.

3. Triple surveillance: from tracking occurrence to tracking the entire causal chain

One often used definition of public health surveillance is as follows: the *ongoing, systematic, and timely* assessment of a health condition, aimed at generating information that is used for action (Thacker et al., 2012). Action may include interventions to prevent or mitigate adverse health effects, such as immunizations to prevent serious infectious diseases or folic acid to prevent neural tube defects. In terms of what surveillance could do for rare diseases and congenital anomalies, we propose broadening the scope to *include and integrate the three basic domains of the causal chain:* cause - disease occurrence - health outcomes (Fig. 1). In Mendelian rare disorders (e.g., MCAD deficiency) the cause is the mutation in both alleles, the occurrence is MCAD deficiency (biochemically and clinically), and the outcomes can go from metabolic acidosis to death in the course of the acute decompensation, typically at the time of fasting with intercurrent illness. For congenital anomalies, the established causes can vary from smoking to maternal diabetes to folate insufficiency, each with its own chain of dependent disease occurrence and health outcomes (Fig. 1).

Historically, for congenital anomalies the focus of surveillance has been disease occurrence. However, if one is able to include the three components of the causal chain in systematic, ongoing surveillance activities, this can add value to in several ways. By tracking the causal

Table 3
Examples of similarities and differences in programs and priorities related to birth defects and rare diseases.

	Birth Defect Programs	Rare Disease Programs	Comment
Surveillance, epidemiology	+ + +	−/+	Major gaps in rare diseases
Diagnosis	+	+ + +	Major focus in rare diseases Rare diseases may present/dx late
Causation	+/+ +	+ + +	special studies in birth defect programs
Outcomes	+	+ + +	special studies in birth defect programs
Treatment	−/+	+ + +	Major focus for rare diseases (research, industry)
Support	Public Health	Research, Industry, Patients	Industry for therapies; vocal RD patient advocacy groups
Legal authority	Mostly public health	Mostly by patient consent	May vary
Main driver	Public health departments, limited clinician involvement	Academic centers, clinically driven	Some BD programs are more clinically oriented than others

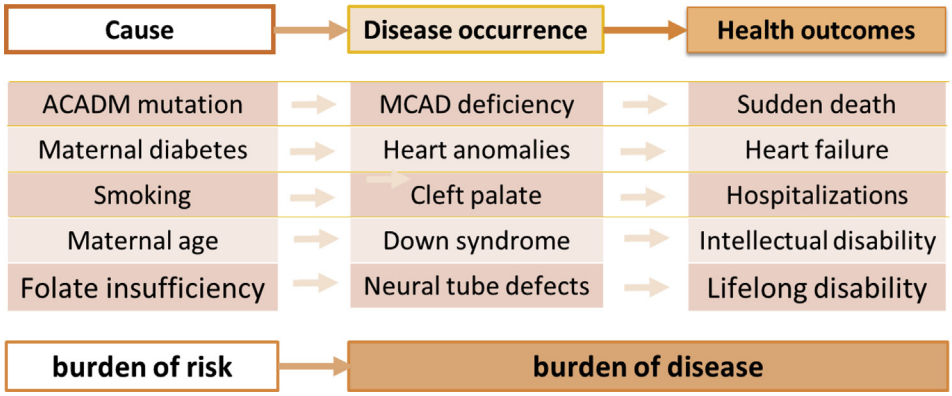

Fig. 1. The concept of causal chain and implications for surveillance of rare diseases and congenital anomalies.

exposure, for example, one can directly and more quickly assess primary prevention interventions compared to having to wait of the outcome to occur. For example, tracking diabetes and smoking in women of childbearing age, one can directly assess the effectiveness of risk-reduction interventions without necessarily waiting years to assess rates of cleft palate, for example. Tracking upstream causes can also more quickly detect gaps such as health disparities (e.g., ineffective strategies in some population groups) and in doing so, accelerate remedies.

Adding health outcomes to surveillance is of fundamental importance for both rare diseases and congenital anomalies. Documenting health outcomes such as morbidity, hospitalizations, quality of life, and mortality provides a much more precise and realistic assessment of the health impact of these conditions, which is often disproportionately higher than its prevalence in the population due to the burden of illness and care associated with many such chronic conditions. This information in turn can be a powerful argument for policies aimed at improving the diagnosis and care of these conditions. A detailed example of this approach has been recently published (Botto and Mastroiacovo, 2018).

4. Putting triple surveillance into practice

Massive Opportunities for Improvement. The main argument here is that surveillance has massive margins of improvement as a force to promote prevention and care. The triple approach strategy aims at effectively combining the emphasis on prevention (by tracking causes/risk factors), assessment (by documenting the ongoing epidemiology of occurrence) and care (by tracking outcomes). To be effective, such system must integrate the three components efficiently. This is important everywhere, but especially in low-resource settings, and emphasizes the necessary focus on streamlined data collection ('no recreational data collection') and broader data use, that is, not only for administrative statistics but also for clinical care.

One must also recognize the several challenges to implementation. Some are operational – e.g., cost, organization, and training – others are intrinsic to the nature of the conditions themselves – the ability to diagnose rare or new disorders, requiring advanced technologies and clinical follow up. Some challenges are also systemic, in the sense that they require collaboration and data sharing between groups that historically may have not worked together closely – public health departments and industry, epidemiologists and clinicians, hospitals and administrative offices.

Some others are technical. A few examples are illustrated in Table 4, to underscore the specific challenges related to surveillance of rare disorders and their incorporation in the joint surveillance with congenital anomalies. For example, case finding will require multiple sources, including specialty clinics for rare genetic conditions. These sources need to be assessed for their value, because every piece of data is expensive for the system. Case ascertainment will benefit from having clinical champions in key institutions, because rare and complex disorders require careful and complete clinical description as well as quality information on health and outcomes, to ensure that each case of rare disorder adds significantly to the body of knowledge. An advantage of rare disorders for surveillance is that they are often diagnosed and followed in a few highly specialized centers. So long as one is able to know residency, a minimum assessment of prevalence can be determined by including such few centers in a given region or country. This is at variance with surveillance of congenital anomalies, for which including tertiary centers can often be a source of systematic ascertainment bias if not adequately prevented and controlled. Finally, coding and classification are an ongoing challenge for rare disorders. ICD systems (International Classification of Diseases, by the World Health Organization) are only broadly useful for congenital anomalies but are even more limited in their ability to precisely code and classify many rare disorders. ICD 10's coding system is reasonably specific for some inborn errors of metabolism (e.g., fatty acid oxidation disorders, E71.3; MCAD deficiency E71.311) but for many other rare disorders there is no specific code so that conditions with widely divergent presentations and outcomes are often lumped in the same group. OMIM (Online Mendelian Inheritance in Man) has a useful system of codes, but it can be confusing to use depending on whether one is coding the phenotype or the genotype, depending on the level of information on a specific case. Orpha codes (Orphanet) has what appears to be a promising approach and tends to be increasingly used in practice. Finally, HPO (human phenotype ontology) codes are now being used in many rare disease clinics and could be a powerful tool to describe the complex phenotypes associated with rare disorders, functioning as a complementary approach to other systems when systematically documenting specific presentations.

An important further consideration is feasibility. It is reasonable to suggest a stepwise approach to triple surveillance, tailored to local goals and resources, so that the processes are practical, efficient, and scalable in the local setting. First, it will be crucial to use what is already available. Where some form of surveillance or registry is already in operation, it should be leveraged, even if somewhat limited. For example, one can start with convenient samples of hospitals and clinic, with initially limited follow up, and perhaps with a few additional sources of ascertainment, such as rare disease programs and specialty clinics. These sources can provide relatively fast if incomplete information on minimal occurrence and health outcomes. For tracking causes or risk factors, a similar approach can be used. Simple surveys that can be done quickly and repeated quickly could be good enough to track risk factors such as maternal smoking, diabetes, folic acid use, or folate blood concentration.

These systems can be expanded through collaboration and focused strategies. Obviously one needs to be realistic. There needs to be a basic infrastructure, with a civil register, health records, sufficient training, advocacy support, and ideally high complexity facilities with diagnostic capacity. Leveraging registries for rare disease in academic centers

Table 4
Selected technical issues in surveillance of rare diseases and congenital anomalies.

Focus	Possible Modalities	Requirements and Issues
Case finding/notification	multiple vs. single source	Best if complementary: labs, specialty clinics Capture wide age range: infant, pediatric, adult Cost-effective: cost per case yielded
Case ascertainment	active vs. passive vs. hybrid	Hybrid systems with champions preferred because of clinical detail and complexity Clinical case review by experts
Window into source population	Population-based (all area residents) vs. facility-based (all seen in facility)	Both might work, so long as residency is known. Including specialty and tertiary-care facilities important because typically where rare diseases are identified and treated. Even minimal estimates are important
Coding and classification	ICD10 vs. Orpha Codes vs. OMIM codes vs. HPO terms	ICD codes not sufficiently specific for most rare diseases. Orpha codes detailed and specific. OMIM numbers can be challenging in practice depending on whether gene or phenotype(s) are coded. HPO terms specific and useful, ideally used to describe all phenotypes, as complement to coding

Note: ICD, International Classification of Diseases; OMIM, Online Mendelian Inheritance in Man; HPO, Human Phenotype Ontology.

(typically disease-specific) can be a very powerful way to move forward quickly. Developing common strategies and shared plans with rare disease groups and advocates can help generate clear common goals and further support for long term sustainability.

Another important consideration is efficiency. It will be crucial, as the conditions under surveillance multiply, to streamline and avoid 'recreational data collection'. Every piece of data needs to be assessed for its contribution to the final goals and should be used. Ideally, data collection and use is integrated in the clinical workflow, and used by the frontline workers in the clinic to also assess the value of the clinical operations, so as not to burden but rather help clinical care.

As noted, a key emphasis in triple surveillance is the sharing of data and skills for common goals. Sitting on data is waste and cannot be afforded.

Finally, it is important to start simple and build on success. It is entirely reasonable and in fact advisable to start with a few important rare diseases and congenital anomalies and build on that experience and success. Examples of such conditions include, as noted, disorders detected by newborn screening (e.g., inherited errors of metabolism, hypothyroidism, cystic fibrosis, disorders of immunity, etc), and skeletal dysplasias. Some programs have already started along that road, by combining registries for congenital anomalies and cancer and building on those key collaborations (Stevens et al., 2018). Using a different approach, some congenital anomaly surveillance programs have been expanding over the years to include a broad range of 'developmental anomalies' including metabolic disorders and cystic fibrosis, among others. An example, is the Western Australian Register of Developmental Anomalies, which has been expanding its scope over the years with considerable success (Nembhard and Bower, 2016).

5. Conclusions

In summary, rare diseases and congenital anomalies have important different but also significant many areas of convergence that can be leveraged to help the lives of people. There are many challenges on the path to improve outcomes. These challenges also depend on local situation, resources, and priorities. Strategies for improvement exist, as noted, but require serious commitment and planning – however, cooperation and integration is the strategy not only for growth but also, and importantly, for relevance and usefulness.

Thoughtful merging of pediatric rare diseases and congenital anomalies can be the basis for triple surveillance to help improve outcomes. As a framework, it emphasizes, and indeed forces a focus on prevention and care, rather than epidemiology alone. As a system, if appropriately built, it can incorporate over time additional conditions at a reasonable marginal cost. As a collaboration, the system builds on the relative strengths of the world of congenital anomalies and the strengths of the rare disease community, with potential considerable benefits for both. In doing so, surveillance can fulfill its fundamental role, which is being a preferential path to better prevention and care.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2018.06.007.

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