European Journal of Medical Genetics xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

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

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ARTICLE INFO

Keywords:
Rare diseases
Birth defects
Surveillance
Health outcomes
Prevention

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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https://doi.org/10.1016/j.ejmg.2018.06.007
Received 22 March 2018; Received in revised form 22 May 2018; Accepted 10 June 2018

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.