Predicting Dental Caries Outcomes in Children: A “Risky” Concept

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Abstract

In recent years, unprecedented gains in the understanding of the biology and mechanisms underlying human health and disease have been made. In the domain of oral health, although much remains to be learned, the complex interactions between different systems in play have begun to unravel: host genome, oral microbiome with its transcriptome, proteome and metabolome, and more distal influences, including relevant behaviors and environmental exposures. A reasonable expectation is that this emerging body of knowledge can help improve the oral health and optimize care for individuals and populations. These goals are articulated by the National Institutes of Health as “precision medicine” and the elimination of health disparities. Key processes in these efforts are the discovery of causal factors or mechanistic pathways and the identification of individuals or population segments that are most likely to develop (any or severe forms of) oral disease. This article critically reviews the fundamental concepts of risk assessment and outcome prediction, as they relate to early childhood caries (ECC)—a common complex disease with significant negative impacts on children, their families, and the health system. The article highlights recent work and advances in methods available to estimate caries risk and derive person-level caries propensities. It further discusses the reasons for their limited utility in predicting individual ECC outcomes and informing clinical decision making. Critical issues identified include the misconception of defining dental caries as a tooth or surface-level condition versus a person-level disease; the fallacy of applying population-level parameters to individuals, termed *privatization of risk*; and the inadequacy of using frequentist versus Bayesian modeling approaches to derive individual disease propensity estimates. The article concludes with the notion that accurate caries risk assessment at the population level and “precision dentistry” at the person level are both desirable and achievable but must be based on high-quality longitudinal data and rigorous methodology.

Keywords: risk assessment, pediatric dentistry, disease susceptibility, evidence-based dentistry, oral health, systems biology

Introduction

A substantial body of knowledge on the fundamental causes and the proximal and distal determinants of common oral diseases in children now exists. “Precision dentistry” is the logical next step following the major advances in the science and practice of dentistry—providing optimal, customized oral health care according to individuals’ specific oral health needs is an ambitious but achievable goal.

Notwithstanding the rapidly increasing scientific and scholarly activity and the dissemination of research findings, substantial gaps remain in the evidence base for common oral conditions and procedures among children (Mejäre et al. 2015). Even where evidence exists, its translation to action and meaningful improvements in population oral health are incomplete or slow (Casamassimo et al. 2014). The translational gap is an important threat to the practice of evidence-based dentistry (Sbaraini et al. 2013). Clinicians naturally desire the best possible clinical (e.g., maintenance of a caries-free dentition) and subjective (e.g., optimal oral health-related quality of life) outcomes for those who are under their care. Professional and academic bodies such as the American, European, and other International Academies of Pediatric Dentistry support practitioners by producing and disseminating clinical guidelines and recommendations based on the best available evidence. Often, these guidelines include clinicians’ judgment or expert opinion

in the decision-making algorithms. For example, the latest dental sealants guidelines of the American Academy of Pediatric Dentistry (AAPD) (Crall and Donly 2015) reiterate Feigal’s (2002) notion that “presently, the best evaluation of risk is done by an experienced clinician using indicators of tooth morphology, clinical diagnostics, caries history, fluoride history, dental care history, and present oral hygiene.” Although clinicians’ “gut feeling” assessments can indeed be as (or more) valid predictors of clinical outcomes than more “objective” systems (Disney et al. 1992), this is a clear illustration of the insufficiency of the available evidence base and translational efforts in guiding clinical decision making in a precise manner.

This article focuses on early childhood caries (ECC) and critically reviews available approaches and tools to inform prediction of ECC development and guide clinical decision making. To this end, it first provides a concise summary of

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fundamental considerations about the disease; it reviews current caries risk assessment approaches and tools, discusses issues with existing methods, and offers recommendations for improving the validity and efficiency of current approaches and directions for developing new ones.

ECC: Fundamental Considerations

Dental decay, including ECC, is a person-level disease (International Statistical Classification of Diseases and Related Health Problems–10, code K02-) wherein acid produced from carbohydrate fermentation by a dysbiotic supragingival microbiome (biofilm) results in demineralization or destruction of susceptible tooth surfaces (Selwitz et al. 2007). ECC is defined as “the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to caries), or filled tooth surfaces in any primary tooth in a child under the age of six” (Drury et al. 1999). The term *caries* is frequently used to describe the clinical manifestation of disease progression (Swedish Council on Technology Assessment in Health Care 2008). However, the disease is best understood as an unfavorable shift of the natural demineralization-remineralization balance (Featherstone 2004) at the enamel-biofilm interface. The disease process is unobservable. Similar to peptic ulcers being the clinical manifestation of a sustained microbial-biochemical imbalance in the stomach or duodenum, carious lesions (ranging from early, subclinical stages to frank cavities) are the clinical manifestation of caries, understood as a disease.

The etiology of ECC is obviously complex and can be viewed from multiple standpoints: molecular/biochemical, microbiological, behavioral, social, health system, and even political. Comprehensive models that depict these multilevel influences on children’s oral health (Fisher-Owens et al. 2007) and related disparities (Lee and Divaris 2014) exist. Recently, Seow (Kim Seow 2012) introduced a unifying conceptual model connecting the social environmental, maternal, and child risk factors involved specifically in ECC. These models are excellent representations of proximal and distal determinants of ECC, including major influences on the incidence of ECC at the population level (e.g., family education and socioeconomic disadvantage).

Diet and particularly sugar intake have recently reemerged as major influences on caries incidence at the population level (Meyer and Lee 2015; Sheiham and James 2015). There is substantial evidence supporting the role of free sugars as the primary necessary factor in the development of dental caries; however, cariogenesis is observed even at very low sugar intake levels, whereas eradicating simple sugars at the population level is a noble but distant goal. Prospective studies provide additional evidence on potential ECC risk factors, including feeding practices (Chaffee et al. 2014; Chaffee et al. 2015), consumption of sugar-sweetened beverages (Park et al. 2015), and other sociobehavioral factors (Peltzer et al. 2014). However, these population-derived determinants are conceptually and practically different from the causes of individual cases (Rose 1985). In fact, understanding the incidence of individual ECC cases and the answer to the question “why this child developed ECC at this moment in time” require knowledge of the specific set of causal factors in play. Determination of causality can be elusive. Moreover, the mechanics of determining causes of

individual cases, including the identification of sufficient or necessary causes (often called “causal pies”), are fundamentally different from identifying associations with disease incidence in the population (Rothman et al. 2008).

Current Approaches: Caries Risk Assessment

The recognition of the multifactorial etiology of dental caries led experts to quickly move into the joint consideration of multiple risk factors while attempting to maintain parsimony and clinical applicability (Newbrun and Leverett 1990). Several excellent systematic reviews, critical summaries, and perspectives on the topic of caries risk assessment have been reported by Mejäre et al. (2014), Twetman et al. (2013), Gao et al. (2013), Tellez et al. (2013), Carson (2013), Twetman and Fontana (2009), the Swedish Council on Technology Assessment in Health Care (2008), and Fontana and Zero (2006). Current discussions and efforts toward evidence-based decision making for caries management in children are summarized in a recent conference summary paper by Slayton (2015).

It is common ground that evidence available on the validity of a number of existing systems for caries risk assessment is limited and weak. The utility of existing systems, including Cariogram (Hänsel Petersson et al. 2002; Holgerson et al. 2009) and those developed by the AAPD (2013), the American Dental Association (ADA 2015), the American Academy of Pediatrics (AAP 2015), and the National University of Singapore (NUS-CRA; Gao et al. 2010), is categorically limited among preschool children, with the “usual suspect,” baseline caries experience, being the best predictor of future disease progression (Swedish Council on Technology Assessment in Health Care 2008; Twetman and Fontana 2009; Tellez et al. 2013; Twetman et al. 2013; Mejäre et al. 2014).

Gao et al. (2013) conducted a head-to-head comparison of multiple assessment tools finding the NUS-CRA as the superior model among Hong Kong 3-y-olds, a population group wherein 89% of participants experienced a positive 12-mo caries increment. Holgerson et al. (2009) showed that Cariogram may not be “particularly useful in identifying high caries risk patients in a low-caries community.” Although further validation and refinement studies will likely lead to improvement of these approaches, currently they cannot be used to guide the design of precise personalized care. However, it is important to note that caries risk assessment tools have excellent pedagogical value, can serve as a basis for discussion, and greatly aid family oral health education. Moreover, they can serve as guides for public policy, allocation of resources in vulnerable segments of the population, design of dental public health programs, and the identification of common risk factors with other conditions (Sheiham and Watt 2000).

Issues with Existing Approaches of ECC Development Prediction

Privatization of Risk

Risk is a population parameter that can be estimated directly from prospective cohort studies and quantified using various

Figure 1. Schematic illustration of individual variations in early childhood caries (ECC) susceptibility within ECC risk groups. Risk has dimensions of a probability often expressed as a fraction over time or categorically (e.g., low, moderate, and high) at the population level; however, children's individual diagnoses can vary between only 2 statuses, ECC case or healthy. Importantly, individual children within the same "risk group" have varying causal risk sets ("pies"), preventing the personalization or privatization of risk (as discussed by Rockhill 2001) and the predictive ability of traditional, population-level risk factors at the person level. Upstream determinants (e.g., socioeconomic factors) are the major influences on the population incidence of ECC, with more proximal factors (e.g., simple sugars, as discussed by Sheiham and James 2015) being important risk factors. As illustrated, children stop being part of the at-risk population when they develop active disease because the disease is defined at the person level; however, they can return to the at-risk group if they do not have active disease. In a similar fashion, they are not at risk when they do not have susceptible tooth surfaces and can return to the risk pool when they acquire new susceptible surfaces (e.g., permanent teeth). It is also depicted that children can change risk category at any time.

measures, including incidence density and cumulative incidence (Slade and Caplan 1999). Cumulative incidence is most frequently used to communicate risk in the oral health domain, as it is a simple fraction expressed over a specific time frame

(e.g., 25% likelihood of ECC development during the first 4 y of life). Although frequently interpreted as such, risk does not communicate the likelihood of individual case occurrence; an individual will either be a case or a non-case (Colditz 2001), but her or his status is simply unknown at baseline (Fig. 1). In other words, risk is not transferable to individuals and cannot be predicted. Rather, risk can be estimated for populations or population subgroups, using longitudinal observations or counterfactual arguments.

The fallacious attempt to transfer and apply risk estimates or population risk factors to individuals is termed the *privatization of risk* (Rose 1985; Rockhill 2001). This is both inefficient and can be misleading, because most risk factors "are neither necessarily nor sufficiently causal at the individual level" (Gori 2001). This explains why ECC risk factors consistently and strongly associated with caries prevalence (or incidence) in large population studies are poor predictors of individual case occurrence.

Outcome Definition

Another major issue that appears to hamper the validity of existing tools is the implicit consideration of dental caries as a tooth-surface condition versus a person-level disease. As mentioned above, the disease process is unobservable to the clinician and de facto precedes the development of its clinical manifestation (e.g., a white spot lesion). The most striking illustration of this issue is the virtually universal notion that "the best predictor of new caries is previous caries experience," wherein existing disease (at the person level) confers progressively increasing impacts on individual, previously healthy, tooth surfaces. In this case, the ambiguous use of the term *caries* has major implications for risk assessment and prediction. If the disease is correctly defined at the person level, risk is not applicable when an ECC diagnosis is made—the disease

is already present. Instead, if tooth surface-level predictions are of interest, then a detailed ascertainment of local factors and individual carious lesion development propensities must take place for each surface or type of surface (Fig.

Figure 2. Schematic illustration of varying tooth surface-level susceptibilities within a population group estimated to have relatively homogeneous (e.g., moderate) early childhood caries (ECC) risk, within the context of proximal causes and distal determinants of ECC development. Susceptibilities of tooth surfaces vary individually and may be grouped in biologically informative clusters (as discussed by Batchelor and Sheiham 2004; Shaffer et al. 2013): case A depicts the dentition of a child with highly susceptible upper anterior smooth surfaces, B reflects high pit and fissure susceptibility, and C an overall uniform moderate susceptibility. Panels D and E illustrate the potential of using proximal measures of disease activity and a systems biology approach (discussed by Nyvad et al. 2013) to ascertain precise estimates of disease propensity, which, for example, are likely to vary between upper anterior facial (D) and lower proximal [E] surfaces. Achieving “precision dentistry” warrants a comprehensive understanding of genome influences on various proximal and distal factors (e.g., enamel properties and dental anatomy, saliva quality and quantity, oral microbiome, interactions with fluoride) and an ability to integrate multiple-level ‘omics data (Ritchie et al. 2015) including the environmental influences on the structure and function of the genome (depicted as epigenetic effects). For simplicity, a host of major influences is included in the “Environment” category, including social determinants of health, diet, and other oral health behaviors.

2). Caries susceptibility varies substantially between tooth surface types (Batchelor and Sheiham 2004; Shaffer et al. 2013), but this information is currently not used by caries risk assessment tools.

Proximal Causes of ECC

The overwhelming dominance of “upstream” factors (e.g., poverty) on the incidence of disease at the population level cannot be overemphasized; however, it is equally important to clarify the proximal factors that are the causes of individual cases. It has been long known that dental caries has a substantial genetic component, with heritability estimates ranging between 30% and 76% (Bretz et al. 2005; Bretz et al. 2006; Shaffer et al. 2012). No comprehensive exploration of the human genome for ECC risk loci has been undertaken, but

some initial evidence exists (Shaffer et al. 2011; Stanley et al. 2014). Although most of this initial evidence remains to be validated, plausible genetic associations may influence tooth anatomy and quality, salivary factors, taste preference, immunity, the oral microbiome, and other factors. The genome, along with the oral microbiome (metagenome), and their interactions (transcriptome, proteome, and metabolome) at the tooth surface level (Nyvad et al. 2013; Dige et al. 2014) remain largely unappreciated in caries risk assessment and personalized clinical decision making.

Quantification and Time: The Missing Dimensions

The perception of risk is subjective, contextual (Viscusi 1993), and arguably outcome dependent. Even within the oral health domain, 19% likelihood over a 2-y period may be considered

Table. Recommended Next Steps for the Development of Valid and Efficient Early Childhood Caries (ECC) Predictive and Clinical Decision-Making Aid Tools.

1. Clarify the definition of ECC incidence on the person and its clinical manifestations on individual tooth surfaces, relying on consensus criteria (e.g., International Caries Detection and Assessment and International Caries Classification and Management systems)
2. Incorporate prior knowledge of disease distribution on the population and varying carious lesion development propensities in different tooth surfaces and tooth surface types, including intraoral correlation and clustering
3. Quantify and communicate actual ECC risk and individual propensities over specific time periods (versus high/moderate/low, which are subject to individuals' interpretation)
4. Use Bayesian modeling approaches to efficiently incorporate prior knowledge and communicate intuitive predictive estimates
5. Develop and incorporate "systems biology" preclinical disease markers (microbiome, metatranscriptome, metaproteome, metabolome, etc.) into ECC definition and prediction
6. Develop and validate host genome ECC markers to derive personalized disease propensity estimates
7. Validate models using multiple child cohorts with varying levels of baseline ECC risk

low for dental caries development (Hänsel Petersson et al. 2002), but it is likely an alarmingly high likelihood for most individuals if the outcome was, for example, oral cancer. For this reason, derivation and communication of absolute estimates (e.g., 2-y probability of caries increment or ECC development) are essential. Otherwise, interpretations of low, moderate, and high risk are guaranteed to differ between and among clinicians and families, according to their context and subjective criteria. Finally, it must be underscored that the dimension of time is explicitly included in the estimation and communication of risk and is essential to interpret disease propensities in a meaningful way. With the exception of Cariogram, no other caries risk assessment tool communicates time-at-risk and actual disease propensities explicitly.

Future Directions

Based on the identified issues, several steps are needed to advance ECC risk assessment at the population level and "precision dentistry" at the person level. These are summarized in the Table and expanded upon below. Importantly, all models and approaches will need to be cross-validated among different child cohorts with varying baseline ECC risks, as the tools' predictive properties (e.g., the positive predictive value, which is the likelihood of an individual "testing" positive to actually develop the condition) depend on the prevalence of the disease.

Development and Use of Valid Preclinical Disease Markers

Recent advances in the "systems biology" understanding of dental caries (Nyvad et al. 2013) go beyond the study of individual factors (e.g., salivary pH, fluoride content, or quantification of specific bacterial species) and set the stage for the development of novel approaches in its diagnosis and management. For example, Belda-Ferre and colleagues (2015) recently reported on the oral biofilm metaproteome in a small sample of caries-affected and caries-free individuals. Hart et al. (2011) had earlier reported on the development of childhood caries predictive models using combinations of microbial and proteomic biomarkers.

Accurate and sensitive measurements of metabolic activity and biochemical interactions at the biofilm-enamel interface may soon allow for the definition of ECC endpoints prior to its clinical

manifestation. Similar to the concept of Stephan's curve, a comprehensive understanding of critical elements of the microbiome-host interaction (Bowen 2013) could enable monitoring of disease activity and prediction of clinical outcomes, ideally at the tooth surface level (Nyvad et al. 2013). The development of novel applications for real-time biomarker and disease activity monitoring will certainly facilitate this advancement.

Predicting Person-Level Caries Outcomes

The development of caries risk assessment tools has so far relied on frequentist multivariate models. In this approach, population parameters are first estimated and then used for individual predictions. Above and beyond the fallacies accompanying the privatization of risk, this approach is also inefficient. This inefficiency stems from the traditional departure of frequentist methods from null or otherwise "naive" models until being informed by the observed data. In fact, all parameters (e.g., the effect of tooth brushing twice a day with fluoridated toothpaste) depart from zero and are unbounded to take values from negative to positive infinity. Bayesian models offer vast improvements in this domain, as they can explicitly and efficiently incorporate prior evidence. It has been shown that this improves prediction (Ellison 2004) even if priors are given with relative uncertainty (i.e., noninformative priors).

In terms of informing ECC predictions, a great deal of accuracy can be gained simply by the knowledge of the ECC prevalence in a given population or simply their whereabouts (Strömberg et al. 2012). Behavioral, clinical, or biomarker information can be added to the Bayesian predictive models to derive posterior distributions that are readily interpretable as probabilities. The latter are more relevant to clinical decision making compared with confidence intervals and *P* values (Laurence 2014) derived by frequentist models. For example, Härkäne et al. (2002) used a Bayesian application to estimate caries risk on individual teeth in a large Finnish cohort. More recently, Wenet et al. (2012) used a Bayesian model to study both person- and tooth-level caries outcomes among a cohort of approximately 210 initially caries-free children, participating in the Center for Oral Health Research in Appalachia Study.

Deriving personalized predictions needs to be founded on detailed monitoring of individual tooth surfaces, for example,

emergence of new teeth that may be most vulnerable in the immediate post-eruptive period (Swedish Council on Technology Assessment in Health Care 2008; Mejre et al. 2014). Existing risk assessment tools are naive with regard to what tooth surfaces are susceptible to develop carious lesions. Consider the extreme scenario of a 4-y-old child with her or his entire primary dentition restored with intact full coverage restorations or “treated” with full-mouth extractions. Caries susceptibility is zero. Nevertheless, traditional caries risk assessment tools will likely classify this patient as high risk due to history of disease, possible deleterious behaviors, cariogenic bacterial counts, and so on. In the same case, emergence of the first permanent molars at the age of 6 will be a major turning point in disease susceptibility—new surfaces are now susceptible. In addition, individual propensities for ECC development (or new carious lesions) are not constant. One may reasonably expect that a child’s ECC propensity is decreased after she or he establishes a dental home and initiates preventive dental care, including regular recall visits and fluoride varnish application.

Along the lines of providing “precision dentistry” at the tooth surface level, substantial recent progress has been made in techniques and approaches available to monitor the activity or progression of individual carious lesions, including fiber-optic transillumination, electric impedance methods, and quantitative light-induced fluorescence (Ferreira Zandon et al. 2013; Fontana et al. 2014). It is important to note that detailed surface-level carious lesion staging and management protocols such as the International Caries Classification and Management System (Pitts and Ekstrand 2013) include explicit patient-level assessments as part of the disease management algorithm, underscoring the importance of precise diagnoses at the person level.

Utilization of Informative Heterogeneity, Clustering, and Correlation

To inform tooth surface-specific predictions and decision making, analytical approaches should take into consideration both the varying propensity of lesion development between surfaces, the potentially informative clustering of surface-type groups, and the multilevel correlation of tooth surface-specific outcomes (Batchelor and Sheiham 2004; Divaris et al. 2013; Shaffer et al. 2013). For example, facial surfaces of maxillary anterior teeth are usually the first teeth to show evidence of the disease (Slayton 2015), whereas posterior approximal surfaces are at higher risk after the development of posterior contacts. In a recent report, Mutsvari et al. (2013) describe the development and testing of a multilevel model accounting for the special distribution and multilevel (surface/tooth/intraoral) correlations of carious lesions, based on Bayesian inference.

Conclusion

Although the existing caries risk assessment and ECC prediction tools have limited practical clinical utility, they serve as a

valuable resource in dental education (training of clinicians) and facilitate communication with patients and their families. In addition, they can serve as guides for the development of public health programs and the allocation of resources in vulnerable segments of the population. The development of valid and efficient tools to inform personalized clinical decision making will have to be based on a clear understanding of differences between “causes of incidence in the population” and “causes of cases,” sizable longitudinal cohorts with high-quality clinical examinations and well-defined disease endpoints, identification of valid preclinical markers of disease activity, and multivariate modeling approaches that enable incorporation of prior information and easily communicable results.

In these exciting times of rapid knowledge generation in the oral health domain, accurate caries risk assessment at the population level and “precision dentistry” at the person level are both desirable and achievable, but they must be based on high-quality data and rigorous methodology.

Author Contributions

K. Divaris, contributed to conception, design, and data acquisition, drafted and critically revised the manuscript. The author gave final approval and agrees to be accountable for all aspects of the work.

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