





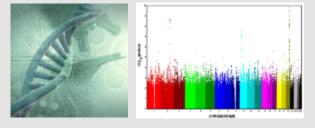


Understanding Early Childhood Oral Health via a Pediatric Precision Health Cohort

Kimon Divaris

Departments of Pediatric Dentistry, School of Dentistry & Epidemiology, Gillings School of Global Public Health, University of North Carolina-Chapel Hill

Kimon_Divaris@unc.edu

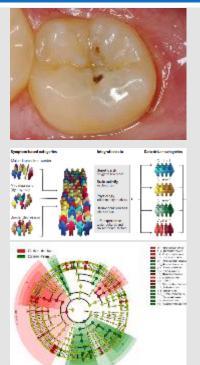




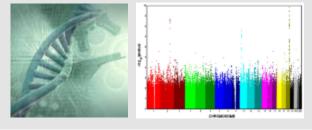




- 1. Early childhood oral health
- The ZOE 2.0 study
- 3. Lessons and early findings
- 4. What next









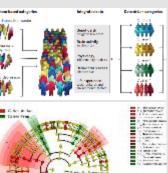


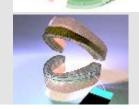


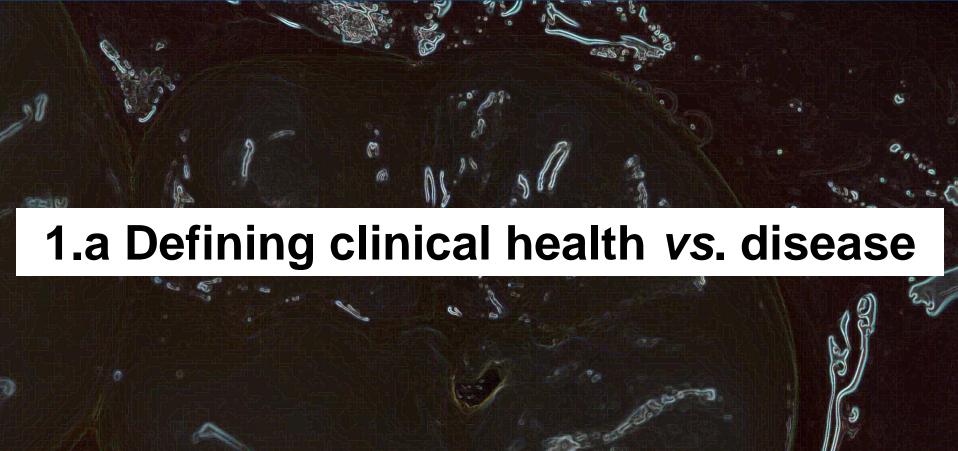
Early childhood oral health

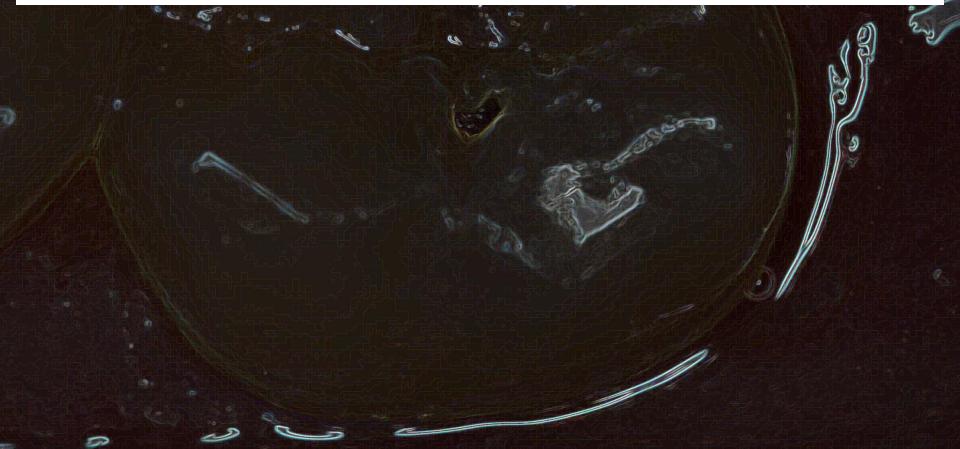
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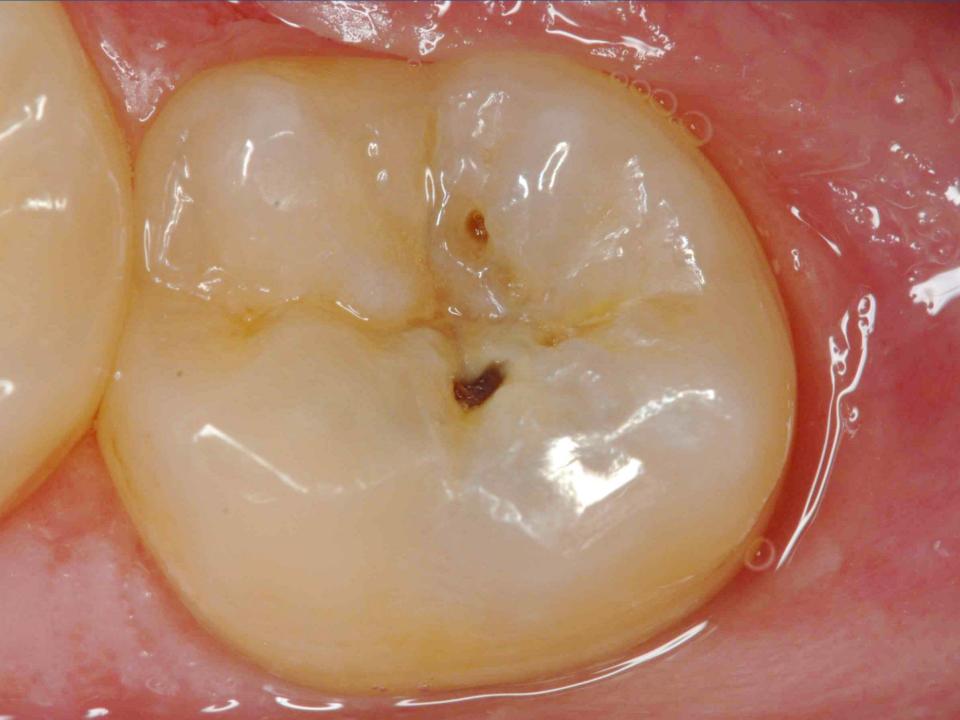










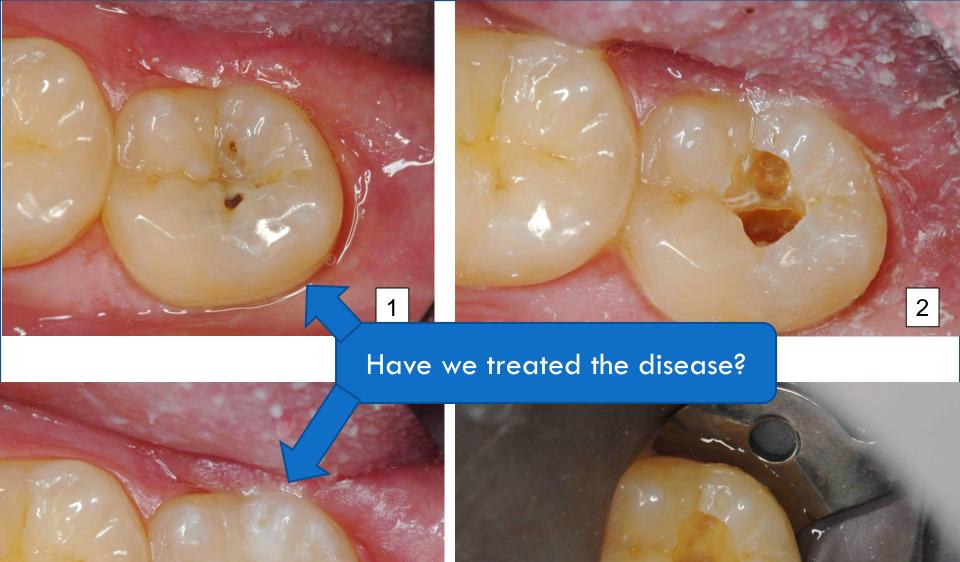


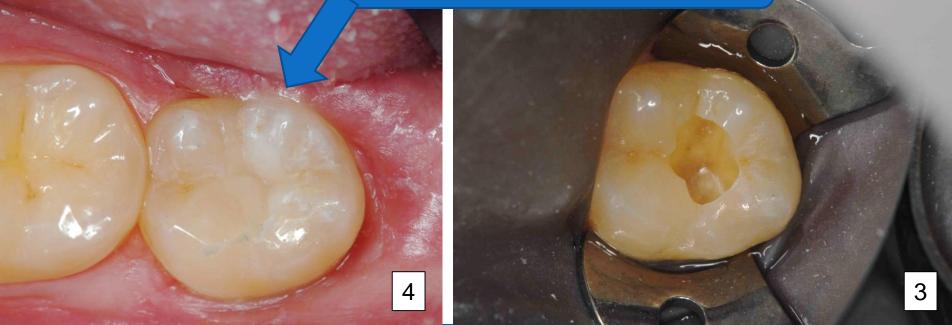


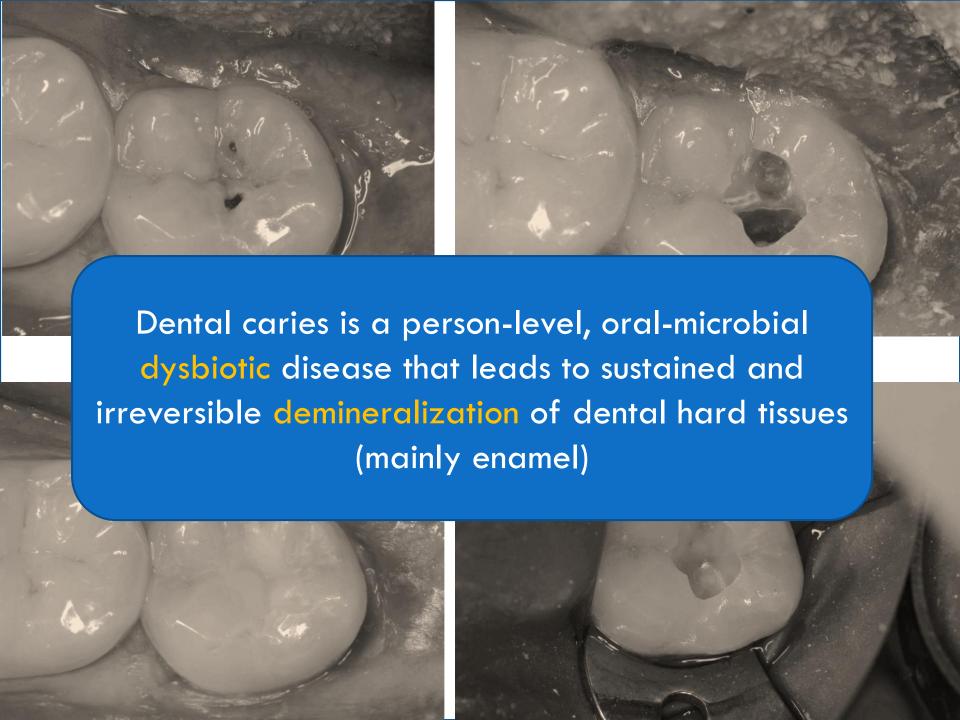


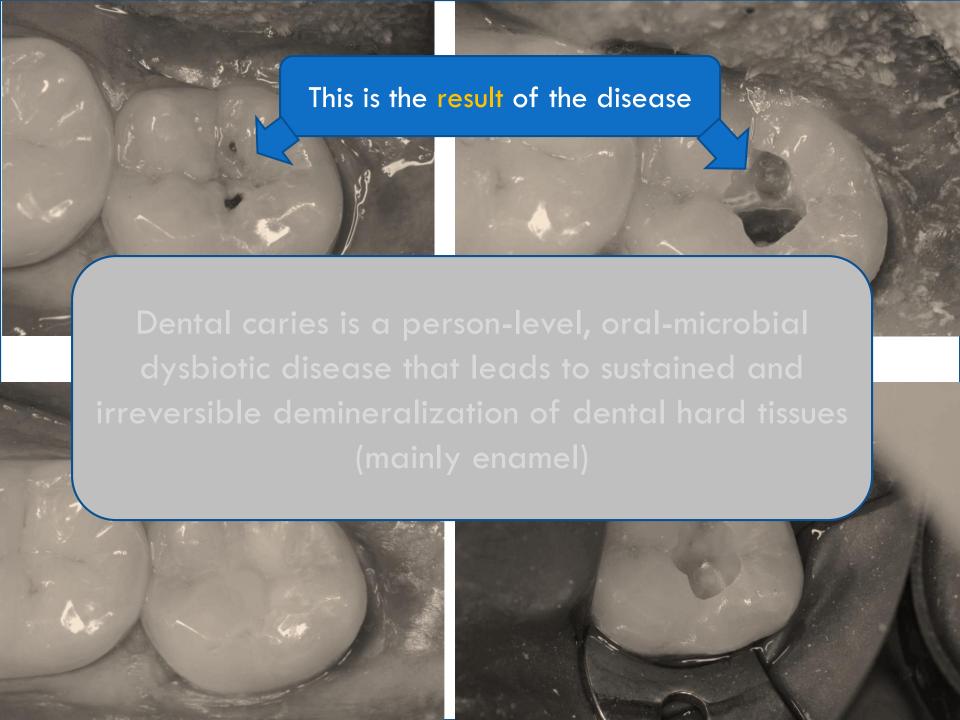
















Dental caries: the disease

EDICAL JOURNAL.

[Oct. 20, 1877.

branes, and but the sequel of the case—the secondary, but not the primary, cause of death. The emaciation and previous history alone remain to guide us; and we are, therefore, forced to the conclusion that it was a case of malnutrition, or, in common parlance, chronic starvation.

WHY DENTAL CARIES IS SO GENERAL, AND HOW TO PREVENT IT.*

By ALEXANDER STEWART, F.R.C.S.Ed.

I HAVE endeavoured in this short paper to show that dental caries has but one proximate cause, and can be largely, if not altogether, prevented by means so readily available that they would no doubt come into general use if generally known; and, as the condition of the teeth now enters, or ought to enter, into the consideration of every case of chronic constitutional disease, the general prevention of dental caries is obviously a subject of great practical importance. It should, I think, find a place in every medical text-book; as dental works are not in the hands of the profession generally, and treating fully the cure of dental caries by operative means they give scant space to its prevention. Further, its operative cure being delegated by them to dental practitioners concerns medical men but little, whereas its prevention as a matter of hygiene concerns them greatly.



1.b Dissecting heterogeneity - precisely

Pre-custom mercilicana contres to postalinates

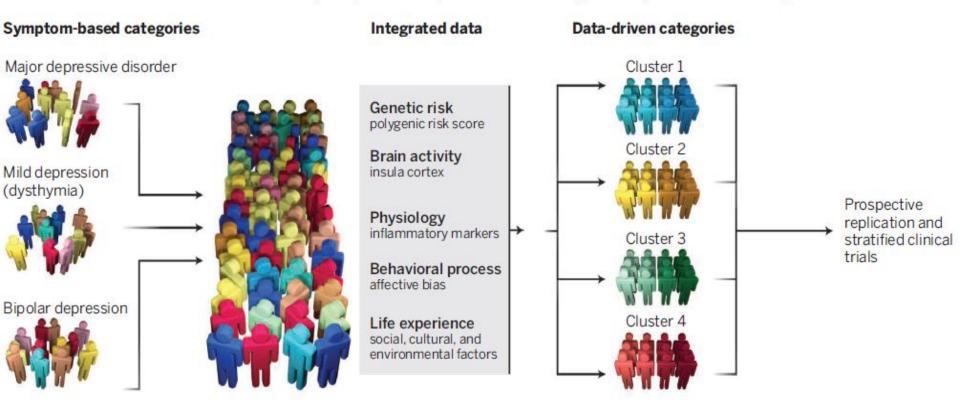
MEDICINE

Brain disorders? Precisely

Precision medicine comes to psychiatry

Deconstructed, parsed, and diagnosed.

A hypothetical example illustrates how precision medicine might deconstruct traditional symptom-based categories. Patients with a range of mood disorders are studied across several analytical platforms to parse current heterogeneous syndromes into homogeneous clusters.



Insel TR, Cuthbert BN. Medicine. Brain disorders? Precisely. *Science*. 2015 May 1;348(6234):499-500.

PERSONALIZED DENTISTRY

Precision Dentistry in Early Childhood

The Central Role of Genomics



Personalized Dentistry

Fundamentals of Precision Medicine

Kimon Divaris, DDS, PhD

magine a world where clinicians make accurate diagnoses and provide targeted therapies to their patients according to well-defined, biologically informed disease subtypes, accounting for individual differences in genetic makeup, behaviors, cultures, lifestyles, and environment. This idea is not as utopic as it may seem. Relatively reKimon Divaris, DDS, PhDa,b,*

KEYWORDS

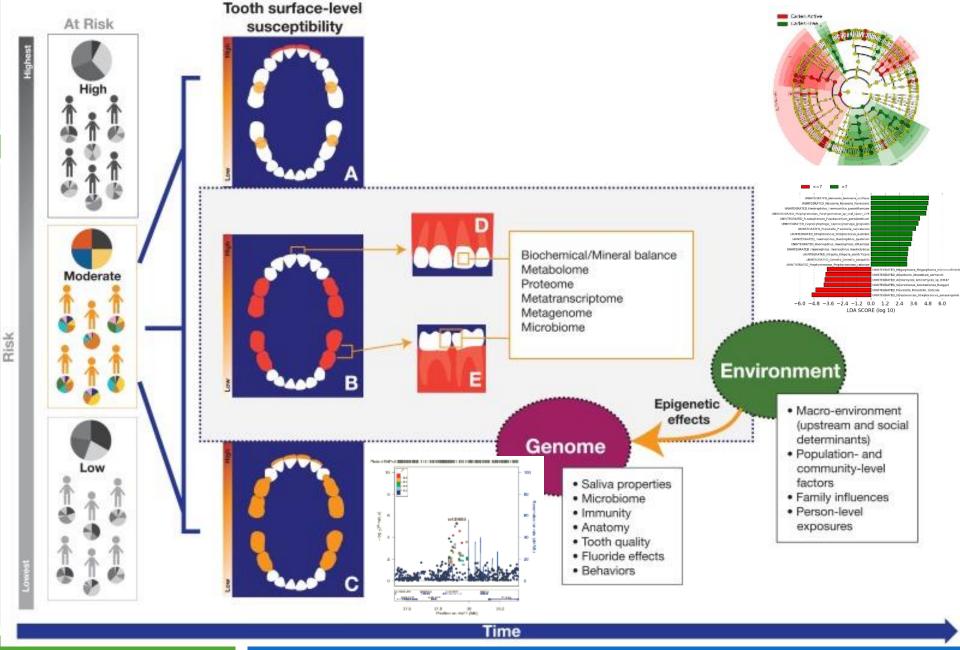
• Children • Oral health • Dentistry • Precision medicine • Genomics

KEY POINTS

- Genomics' role is now well characterized for rare and penetrant developmental traits of early childhood, including craniofacial malformations and developmental defects of dental hard tissues.
- Children have demonstrably varying individual susceptibilities to dental caries; however, specific loci, genes, and implicated pathways, functions, and environmental interactions remain elusive.

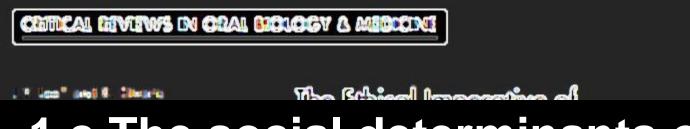
PMID: 29227115

PMID: 28577641



Divaris K. Predicting Dental Caries Outcomes in Children: A "Risky" Concept. *J Dent Res* 2016 Mar;95(3):248-54.

The overwhelming influence of upstream factors



1.c The social determinants of health



PMID: 24189268

Lee JY, Divaris K. The ethical imperative of addressing oral health disparities: a unifying framework. *J Dent Res.* 2014 Mar;93(3):224-30.

The overwhelming influence of upstream factors

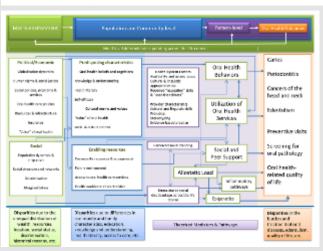
CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

J.Y. Lee* and K. Divaris

The University of North Carolina at Chapel Hill - Department of Pediatric Dentistry, 228 Brauer Hall, Chapel Hill, North Carolina 27599, USA; *corresponding author, jessica_lee@unc.edu

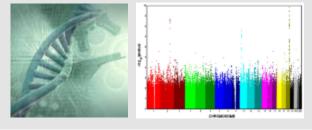
J Dent Res 93(3):224-230, 2014

The Ethical Imperative of Addressing Oral Health Disparities: A Unifying Framework



PMID: 24189268

Lee JY, Divaris K. The ethical imperative of addressing oral health disparities: a unifying framework. *J Dent Res.* 2014 Mar;93(3):224-30.



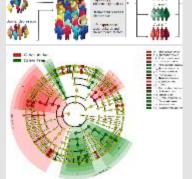






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Zero-Out Early Childhood Caries Genes for Smiles (NIH/NIDCR, 2015-2020)

Community-based genetic epidemiologic study of early childhood oral health among preschool children enrolled in HS (ages 3 and 4)

Ultimate goal is the conduct of a trans-ethnic genome-wide association metaanalysis (GWAS) to identify genetic risk factors (loci) for Early Childhood Caries (ECC)

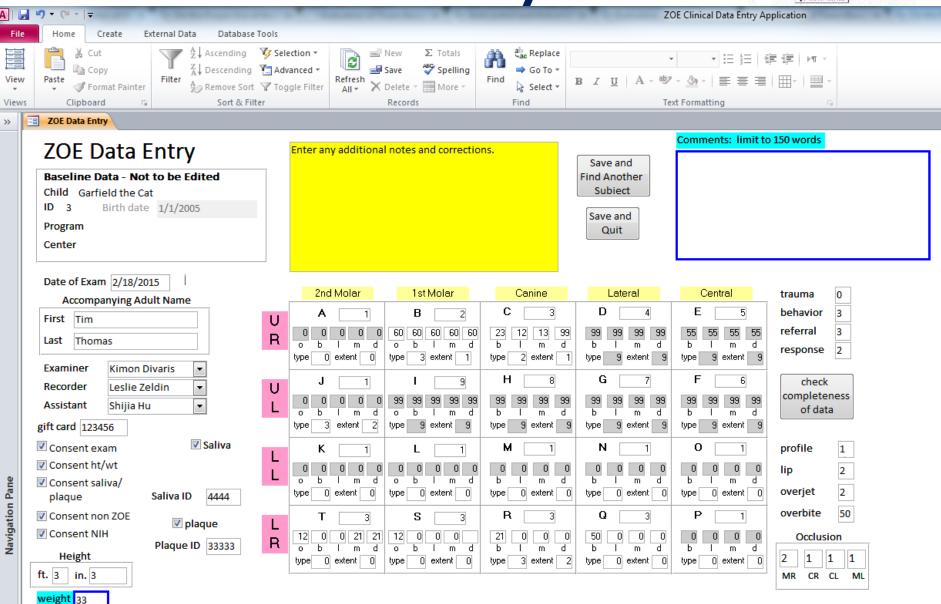
Aim to enroll \sim 9,000 children over a \sim 3-year period to achieve a genotype & phenotype sample of \sim 6,000



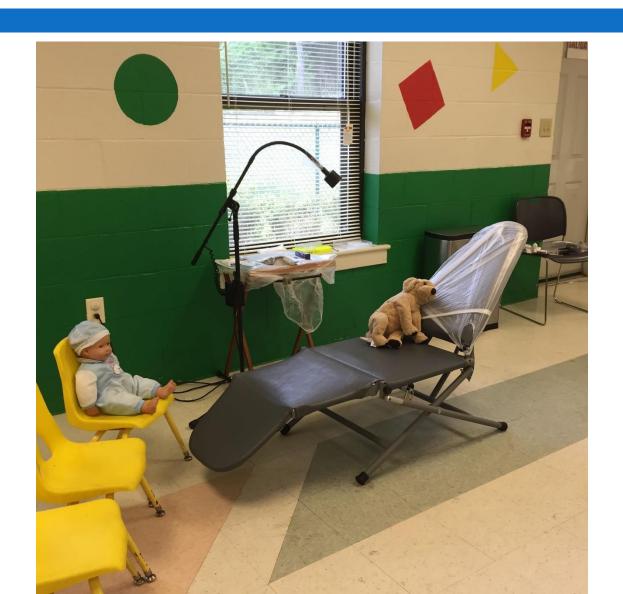
Clinical examination domains [~15' duration]:

- Height, weight, BMI
- Saliva sample (for DNA extraction, biobanking and analysis)
- Microbial plaque samples (for biobanking and future studies)
- \Box EO/IO exam (profile, lip competence, OJ/OB, molar/canine relationships)
- Tooth surface-level caries (ICDAS criteria: healthy, pre-cavitated, cavitated)
 and developmental defects of enamel (simplified epi. DDE index)
- Dental trauma (Ellis' classification)
- Frankl behavior score
- Referral needs (dental home, possible problems, immediate tx needs)









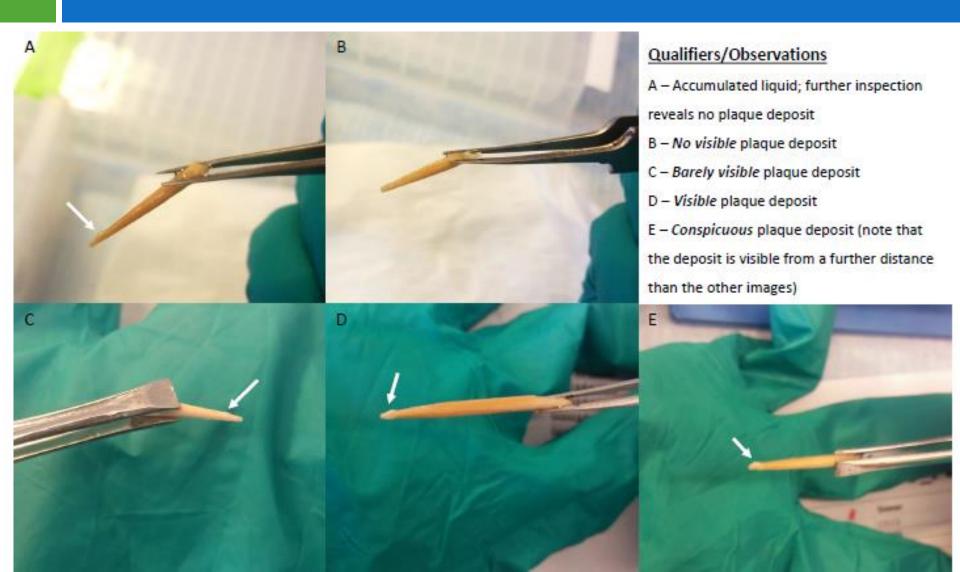


ZERD OUT EARLY CHILDHOOD TOOTH DECAY



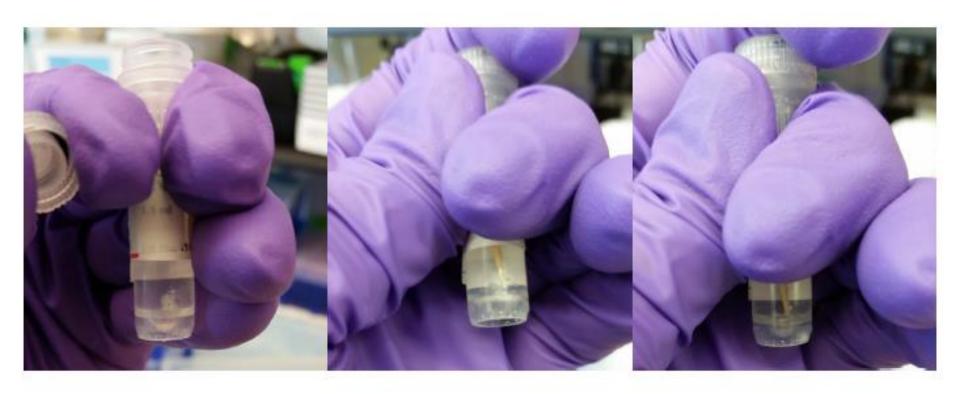


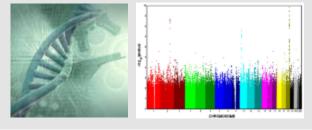
ZERD OUT EARLY CHILDHOOD TOOTH DECAY





Examples of conspicuous pellets in sample vials. No donor identifiers are present in these images.





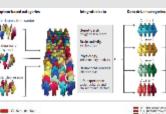


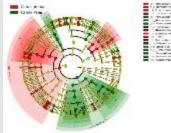


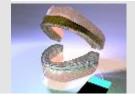


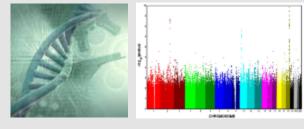
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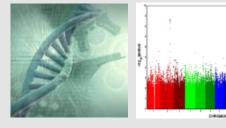








- 1.Logistics
- 2.Community engagement
- 3.Examiner calibration
- 4. Dental caries, obesity, trauma, dental home
- 5. Water testing fluoride
- 6. Genomics
- 7. Methodological contributions
- 8. Biofilm insights
- 9. Community perspectives









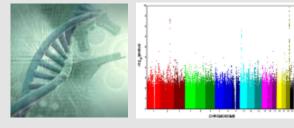
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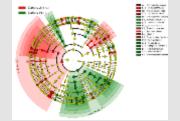
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[1] Ginnis *et al.* **Measurement** of early childhood oral health for research purposes: **dental caries experience and developmental defects of the enamel** in the primary dentition. *Methods Mol Biol.* 2018 forthcoming

[2] Agler *et al.* Protocols, methods and tools for **genome-wide association studies (GWAS) of dental traits**. *Methods Mol Biol.* 2018 forthcoming

[3] Divaris *et al.* The **supragingival biofilm** in early childhood caries: clinical and laboratory protocols and bioinformatics pipelines supporting oral **metagenomics**, **metatranscriptomics and metabolomics** studies of the oral microbiome. *Methods Mol Biol.* 2018 forthcoming







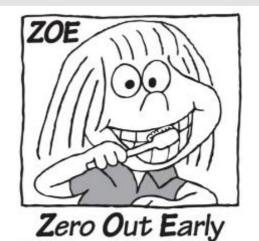


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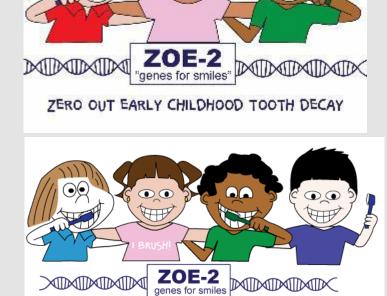
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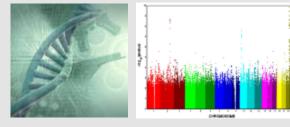


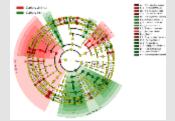


Childhood Tooth Decay



ZERO OUT EARLY CHILDHOOD TOOTH DECAY









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The Partnerships

and the team for such an awesome job.

Due to the connection that our Nutrition Manager, with your organization about Dental Health, we were given a wonderful opportunity to form, I hope, a prosperous and lasting partnership.

The ZOE-2.0 Project Team really made the experience very smooth and instrumental for the children. Some children had never seen a dentist. So, to have your team come into our facilities and perform those dental screenings made children feel safe and comfortable.

The parents were pleased as well; and for the ones that needed some extra care, took the written advice given them from the screening.

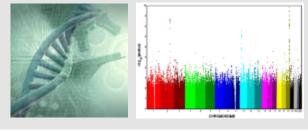
I would certainly encourage other programs to form a partnership with this project. The staff is awesome. They worked with our schedule/timeline. They were courteous, friendly, and professionally down to earth. They were

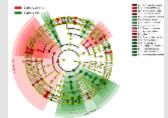
proficient in what they did, and they even had a staff member that could speak to our Hispanic children in their language. The children received a dental health baggie with dental supplies (toothpaste, tooth brush, and instructions on brushing). Parents received an incentive as well. It was well worth this wonderful Team coming and screening our children in their own environment.

I could not have asked for a better Team to have come to my centers and perform the many tasks they did in such a caring and timely manner. My hats are off to them.

Finally, if at all possible, we would love for this Team to do this again next season and even schedule some screenings midyear to catch some children they may enroll after school has started. We would forever be grateful to them. Hope to see ZOE-2.0 Project next season.

Sincerely,









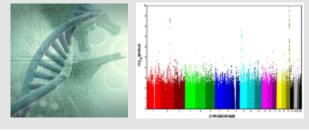
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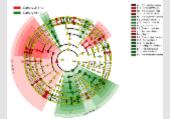
Measuring Preschool-age Children's ICDAS-based Caries Experience: Examiner's Training and Calibration

Ferreira Zandona AG, Ginnis J, Cantrell J, Meyer BD, Slade GD, Divaris K Abstract, AADR meeting, Fr. Lauderdale, March 2018

236 children, 20,317 tooth surfaces for **inter**-examiner agreement median weighted kappa = 0.75

64 children, 5,178 surfaces for **intra**-examiner agreement median weight kappa = 0.79









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<u>Dental caries prevalence</u> (≥1 established/severe lesion, restoration, etc.) = 48% [first 2,490 participants]

Anthropometry:

Normal weight: 69%

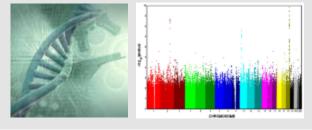
Overweight: 13%

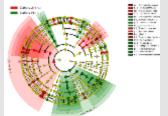
Obese: 9%

Underweight: 9%

Evidence of <u>traumatic dental injury prevalence</u> (pulp exposure, tooth displacement, necrosis, tooth loss)= 4% [first 1,546 participants]

Reported <u>dental home</u> = 81%



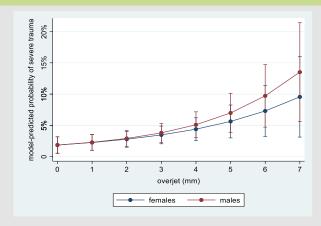


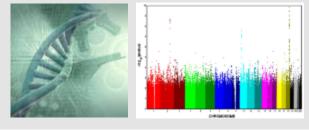


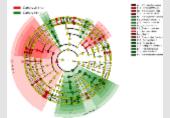


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Association between overjet (mm) and traumatic dental injury











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8 PASOS SENCILLOS PARA PROVEER UNA MUESTRA DE AGUA

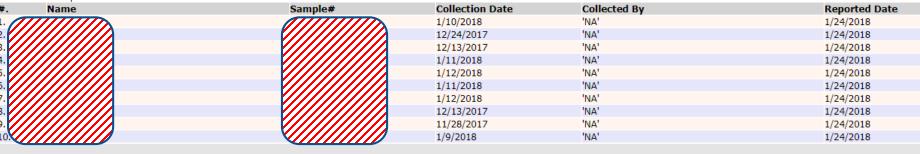


North Carolina State Laboratory Public Health Environmental Sciences - Inorganic Chemistry



InOrganic Sample Results

Click on the sample numbers to view the results.



StarLiMS ID: Date Collected: Time Collected:

Date Received: 11/02/17 Collected By:

Sample Type: Sampling Point: Date of Birth:

Sample Source: Well Water Temp. at Receipt: GPS #:

Sample Description Comment:

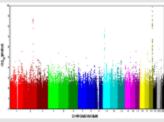
9.19 mg/L Nitrate-N detected in this sample. Please contact ;your local county health department if you would like additional testing for nitrate.

Fluoride (Profile)

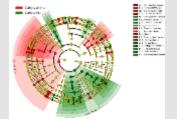
Analyte	Result	Allowable Limit	Unit	Qualifier(s)
Fluoride	< 0.20	4.00	mg/L	

Report Date: 11/15/2017 Reported By:





PAEDIATRIC







Lessons and early findings

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Exploring the genomic basis of early childhood caries: a pilot study

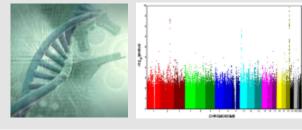
JAMI L. BALLANTINE¹, JENNA C. CARLSON^{2,3,4}, ANDREA G. FERREIRA ZANDONÁ⁵, CARY AGLER⁶, LESLIE P. ZELDIN⁶, RICHARD GARY ROZIER⁷, MICHAEL W. ROBERTS¹, PATRICIA V. BASTA^{8,9}, JASON LUO^{10,11}, MIKAFUI E. ANTONIO-OBESE⁶, DANIEL W. MCNEIL¹², ROBERT J. WEYANT¹³, RICHARD J. CROUT¹⁴, REBECCA L. SLAYTON¹⁵, STEVEN M. LEVY^{16,17}, JOHN R. SHAFFER^{2,4,18}, MARY L. MARAZITA^{2,4,18,19,20}, KARI E. NORTH⁸ & KIMON DIVARIS^{1,8}

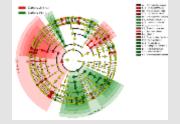
¹Department of Pediatric Dentistry, School of Dentistry, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA, ²Center for Craniofacial and Dental Genetics, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA, USA, 3Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA, 4Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA, 5Department of Operative Dentistry, School of Dentistry, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA, 6Oral and Craniofacial Health Sciences, School of Dentistry, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA, Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA, ⁸Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA, ⁹Biospecimen Processing Facility core, University of North Carolina, Chapel Hill, NC, USA, ¹⁰Lineberger Comprehensive Cancer Center, School of Medicine, University of North Carolina, Chapel Hill, NC, USA, 11 Mammalian Genotyping core, University of North Carolina, Chapel Hill, NC, USA, 12 Departments of Dental Practice & Rural Health and Psychology, West Virginia University, Morgantown, WV, USA, 13Department of Dental Public Health and Information Management, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA, USA, 14Department of Periodontics, School of Dentistry, West Virginia University, Morgantown, WV, USA, 15 Department of Pediatric Dentistry, School of Dentistry, University of Washington, Seattle, WA, USA, 16 Department of Preventive and Community Dentistry, University of Iowa College of Dentistry, Iowa City, IA, USA, 17 Department of Epidemiology, University of Iowa College of Public Health, Iowa City, IA, USA, 18 Department of Oral Biology, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA, USA, ¹⁹Department of Psychiatry, School of Medicine, University of Pittsburgh, Pittsburgh, PA, U

Translational Science Institute, School of Medicine, University of Pittsburgh, Pittsburgh, PA

PMID: 29057527

Ballantine JL, et al. Exploring the genomic basis of early childhood caries: a pilot study. Int J Paediatr Dent. 2017 Oct 23.



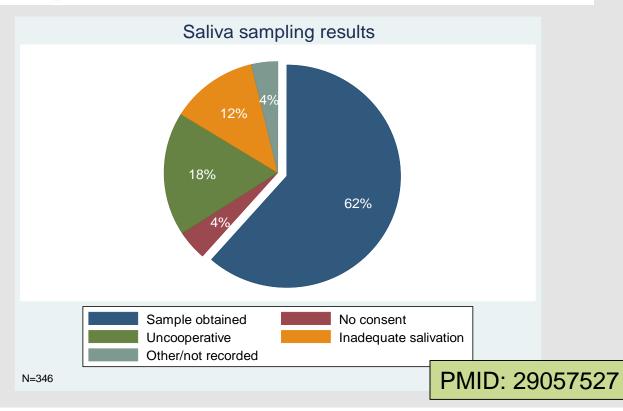




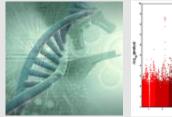


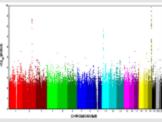
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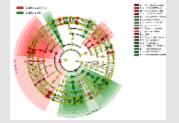
Exploring the genomic basis of early childhood caries: a pilot study



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Statistics in Medicine

Research Article

Received 14 February 2015, Accepted 20 October 2015 Published online 15 November 2015 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6804

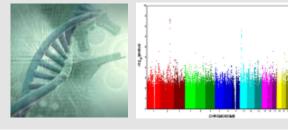
Marginalized zero-inflated negative binomial regression with application to dental caries

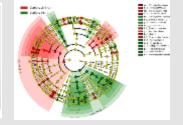
John S. Preisser, ax† Kalyan Das, D. Leann Long^c and Kimon Divaris^d

The zero-inflated negative binomial regression model (ZINB) is often employed in diverse fields such as dentistry, health care utilization, highway safety, and medicine to examine relationships between exposures of interest and overdispersed count outcomes exhibiting many zeros. The regression coefficients of ZINB have latent class interpretations for a susceptible subpopulation at risk for the disease/condition under study with counts generated from a negative binomial distribution and for a non-susceptible subpopulation that provides only zero counts. The ZINB parameters, however, are not well-suited for estimating overall exposure effects, specifically, in

PMID: 26568034

Preisser JS, Das K, Long DL, Divaris K. Marginalized zero-inflated negative binomial regression with application to dental caries. Stat Med. 2016 May 10;35(10):1722-35.









- 1.Logistics
- 2.Community engagement
- 3.Examiner calibration
- 4.Dental caries, obesity, trauma, dental home
- 5. Water testing fluoride
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Metagenomics of Early Childhood Oral Health and Early Childhood Caries

Kimon Divaris, Roach J, Basta PV, Ferreira Zandona AG, Ginnis J, Meyer BD, Hu S, Simancas-Pallares MA, Butz N, Azcarate-Peril MA

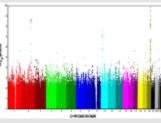
Abstract, AADR meeting, Fr. Lauderdale, March 2018

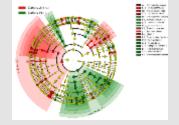
118 children, ages 3-5, whole genome sequencing (**WGS**) shotgun of supragingival biofilm

712 million high-quality reads

Comparisons between 3 groups: **health** (caries-free), disease (**unrestored** caries lesions and **restored** caries lesions)











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RESEARCH ARTICLE

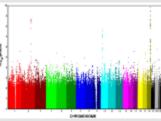
Framing Young Childrens Oral Health: A Participatory Action Research Project

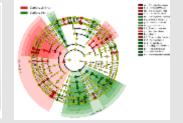
Chimere C. Collins¹, Laura Villa-Torres², Lattice D. Sams¹, Leslie P. Zeldin³, Kimon Divaris^{4,5}*

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PMID: 27548714









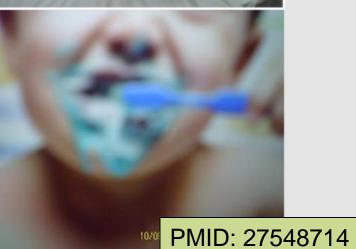


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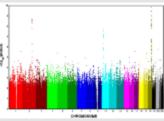


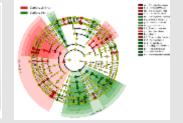










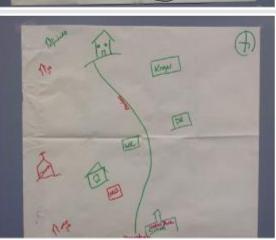




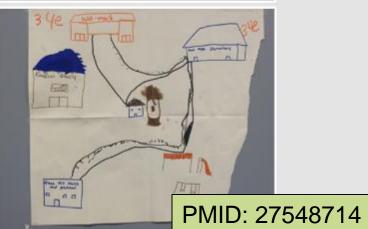


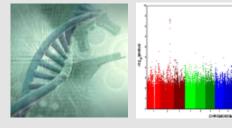
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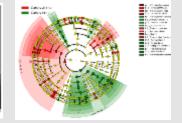
















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Participants' quotes

"It's harder to buy healthier foods, because of the prices".

"We live in a country that subsidizes processed food, and makes the really good stuff expensive".

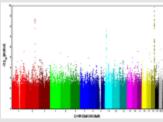
"So often it's just you get in a rush at bedtime, or ... She's getting to be old enough that I say, "Go brush your teeth", and I'm not always in there too make sure that she's really doing it".

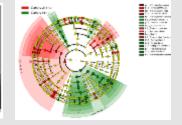
"Accessibility. I'd say that's probably the biggest thing.

"I definitely needed a dentist that's open after 5:00PM...That's the point. To be able to go after school or get the kids to bed and go".

PMID: 27548714











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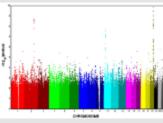
In person interviews with parents of young children

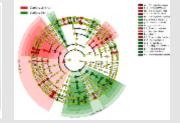
Investigator: [...] If this is easily available by saliva sample and affordable, would you be interested in having genetic testing to obtain health and disease risk information for your child by a physician?

Parent: If you had asked me that two years ago, I [would say no] but since I do have a sick kid, I think the answer to that would be yes.

Becherer and Divaris, unpublished











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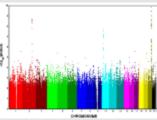
In person interviews with parents of young children

Investigator: [...] The results are in and she tells you that you are a genetically pre-disposed or high-risk to develop condition that can be prevented with changes in your diet and overall lifestyle [...] What would be your reaction?

Parent: I would probably do it. Change my lifestyle. I say probably, because those are all hypothetical. I really like chocolates, but I'm not saying I'll be perfect about it but I would give it a shot anyway for sure.

Becherer and Divaris, unpublished











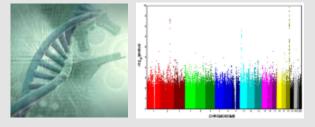
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In person interviews with parents of young children

Investigator: [...] Do you have any ethical or privacy concerns regarding genetic testing for routine health care?

Parent: I do, but I'm not as concerned about that as some of the people I know. I'm not a conspiracy theorist, but I do think that the more information that's out there about you, the more likely that information to be acted or used in a way where it wasn't intended for. I think there is cause for concern. How much concern? I have no idea. Who would be using that information and for what? I don't know. Is it going to be ... We end up with a one payer health care system and the government decides who is and who isn't going to get treatments because of the genetic testing, I think it's possible but not probable.

Becherer and Divaris, unpublished



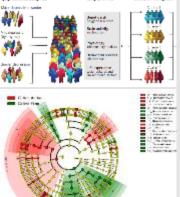




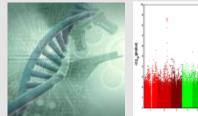


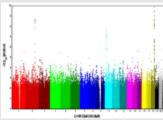
- 1. Early childhood oral health
- 2. The ZOE 2.0 study
- Lessons and early findings
- 4. What next

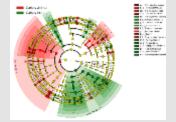














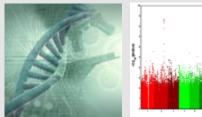


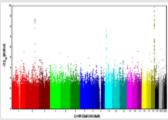
What next

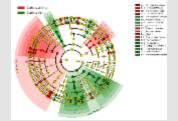
1.Added measures to the current cohort

- 2.Further characterize disease subtypes
- 3.Further understand communities
- 4.Follow-up

- 1. Medicaid claims data
- 2. Qualitative studies among the positive outliers
- 3. Understand HS program/centers influence
- 4. Super-impose contextual factors
- 5. Obtain intra-oral photos
- 6. Conceptualize ways to monitor oral health











Tooth surface status monitoring

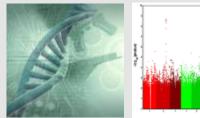


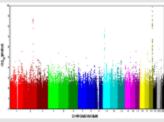
Conceptualize ways to monitor oral health

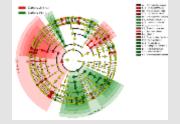


Genomics

Metagenomics (meta-) Transcriptomics Metabolomics











What next

- Added measures to the current cohort
- 2.Further characterize disease subtypes
- 3. Further understand communities

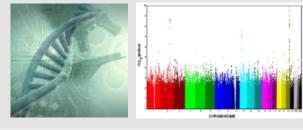
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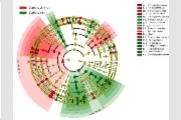
1. Further characterize disease subtypes

- a) Patterns of dental caries lesion development in the primary dentition
- b) Microbial/biochemical signatures

2. Further understand communities

- a) What works, what doesn't
- b) Impact and development of oral health champions
- c) School-based programs
- d) How does precision dental public health look like?









What next

- Added measures to the current cohort
- 2.Further characterize disease subtypes
- 3.Further understand communities
- 4.Follow-up

Primary dentition

Human genome

Supragingival biofilm: metagenomics transcriptomics metabolomics

Behaviors: OH, diet, dental attendance, etc.

Environment: fluoride, contextual (geocoding)

3-4 y.o

2017-18

Others

Mixed dentition

<u>Incident or progressive</u> <u>outcomes</u>

1st permanent molars

Supragingival biofilm, behaviors, environment, expenditures, comorbidities, others

8-9 y.o

Permanent dentition

Incident or progressive outcomes

2nd permanent molars

Periodontal assessment

Supragingival, subgingival biofilm, behaviors, environment, comorbidities, OHRQoL, expenditures, others

13-14 y.o

2022-23 2027-28



The team

Supported by NIH/NIDCR U01-DE025046

53

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