RESEARCH TO ADVANCE CHILDREN’S HEALTH AND WELL-BEING

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I have no conflicts of interest to disclose, except my biases in favor both of children’s health and well-being and of research.
Disclosure

As a federal bureaucrat, if I did have any, I would be spending 10 years in Leavenworth, instead of a lovely few days with you in Aspen.
What’s To Come...

- **Past:** Has research led to any progress in children’s health and well-being?
- **Present:** Why would investments today in research make any difference in children’s health and well-being?
- **Future:** What future could we create for children through research?
What’s To Come...

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Research Changes Children’s Lives

- Because of research and improvements in public health and health care based on research, children’s health and lives have changed...
- And, we have data to prove it...
Overall Decline in Infant Mortality

- U.S. infant mortality rates dropped >90% in the 20th century

Source: CDC
Reduction in Pediatric ALL Deaths

Haemophilus Influenzae

**Figure 1.** Incidence* of *Haemophilus influenzae* (Hi) invasive disease among children aged <5 years, incidence† of Hi invasive disease among persons aged ≥5 years, and number of states reporting Hi surveillance data — United States, 1987–1997§

*Per 100,000 children aged <5 years.
†Per 100,000 persons aged ≥5 years.
§Because of the low number of states reporting surveillance data during 1987–1990, rates for those years were race-adjusted using the 1990 U.S. population.
Reduction in SIDS Deaths

% Back and Side Sleeping

- Pre-AAP recommendation
- Post AAP
- Back to Sleep Campaign

SIDS Deaths per 1,000 Live Births

- 1985: 1.41
- 1986: 1.41
- 1987: 1.37
- 1988: 1.4
- 1989: 1.39
- 1990: 1.3
- 1991: 1.3
- 1992: 1.2
- 1993: 1.17
- 1994: 1.03
- 1995: 1.03
- 1996: 0.87
- 1997: 0.74
- 1998: 0.72
- 1999: 0.67
- 2000: 0.62
- 2001: 0.56
- 2002: 0.57
- 2003: 0.53
- 2004: 0.55
- 2005: 0.54

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The Research World Has Changed

• Many new and emerging research tools and opportunities

Many things can wait; the child cannot. Now is the time his bones are being formed, his mind is being developed. To him we cannot say tomorrow; his name is today.

- Gabriela Mistral
The Pace of Genomics Technologies: We Have Put Moore’s Law to Shame
The Research World Has Changed

- Many new and emerging research tools and opportunities
- For example, genome-wide association studies (GWAS)
GWAS: Unlocking Biology

- An important way to identify genes that play roles in specific common diseases
- This allows identifying individuals who are at increased risk of developing the disease
- Even more powerfully, allows discovering the biological pathways that cause the disease
- 2002: $10,000,000,000 for each disease
- 2007: $800,000 for each disease
Where We Recently Were

- Human Mendelian traits
- All complex traits
- Human complex traits

Number of human Mendelian traits for which molecular basis found

Number of complex trait genes

Year:
- 1980
- 1985
- 1990
- 1995
- 2000
Where Are We Now?
An Example of What We Can Do Now

- Ten years ago, the cause of Crohn’s disease (CD) was unclear; since then, GWAS identified dozens of genomic regions that influence risk for CD.
- Analyses of these regions and new cellular models revealed previously unappreciated, key roles of several specific genes and biological processes in CD.
- Animal models have been developed that accurately model the effects of causal variants in human patients.
- Chemical screens have identified new candidate therapies.
Human Microbiome Project

- An initiative using genomic analysis to characterize the complexity of microbes at individual body sites, and to determine whether there is a core microbiome at each site.
• Largest and most ambitious U.S. long-term study of child health and development ever

• Will follow 100,000 children from birth (or earlier) through age 21

• Longitudinal study of biological and broadly defined environmental factors, such as:
  ○ Air; water; soil; dust; noise; diet; social and cultural setting; access to health care, socio-economic status, learning; etc.

• Resource of rich data with linked environmental and biological samples, not a conventional “study”
Some Recent Societal Changes Are Assets

- A move in many societies towards inclusion and recognizing the rights, contributions to society, and dignity of those with “diffabilities”...
But, Many Health Needs Remain; e.g. ...

- WHO estimates 3.7 million neonatal deaths and 3.3 million stillbirths occur globally each year
- High preterm birth rates
- Many infants with low birth weight suffer from poor cognitive outcome
- Growing rates/epidemics in U.S. of asthma, obesity, childhood onset DM2, cyber-bullying, autism
- Huge racial and ethnic disparities in outcomes
- Too much clinical practice is still not evidence-based
- Etc., etc. ...
Preterm Birth – A Global Problem That Hits Home

10 countries account for >60% of the world’s preterm births

1. India (3.5m)
2. China
3. Nigeria
4. Pakistan
5. Indonesia
6. USA (517,400)
7. Bangladesh
8. Philippines
9. Dem Rep Congo
10. Brazil (279,300)
Autism

Prevalence of Autism Spectrum Disorders in a Total Population Sample

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Eun-Chung Lim, M.A.
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Objective: Experts disagree about the causes and significance of the recent increases in the prevalence of autism spectrum disorders (ASDs). Limited data on population base rates contribute to this uncertainty. Using a population-based sample, the authors sought to estimate the prevalence and describe the clinical characteristics of ASDs in school-age children.

Method: The target population was all 7- to 12-year-old children (N=55,266) in a South Korean community; the study used a high-probability group from special education schools and a disability registry and a low-probability, general-population sample from regular schools. To identify cases, the authors used the Autism Spectrum Screening Questionnaire for systematic, multi-informant screening. Parents of children who screened positive were offered comprehensive assessments using standardized diagnostic procedures.

Results: The prevalence of ASDs was estimated to be 2.64% (95% CI=1.91–3.37), with 1.89% (95% CI=1.43–2.36) in the general-population sample and 0.75% (95% CI=0.58–0.93) in the high-probability group. ASD characteristics differed between the two groups: the male-to-female ratios were 2.5:1 and 5:1 in the general population sample and high-probability group, respectively, and the ratios of autistic disorders to other ASD subtypes were 1:2.6 and 2.6:1, respectively; 12% in the general-population sample had superior IQs, compared with 7% in the high-probability group; and 16% in the general-population sample had intellectual disability, compared with 59% in the high-probability group.

Conclusions: Two-thirds of ASD cases in the overall sample were in the mainstream school population, undiagnosed and untreated. These findings suggest that rigorous screening and comprehensive population coverage are necessary to produce more accurate ASD prevalence estimates and underscore the need for better detection, assessment, and services.

1 in 38 children with autism???

MMWR. 2011:60;42-46
And...

- Even good news can bring bad news in its wake...
Infectious Diseases Get Rarer, But Immune Disorders Get More Common

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

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Just a Few - of Many - Examples...

Children are the world’s most valuable resource and its best hope for the future.
- JOHN FITZGERALD KENNEDY
A Fun Fact: How Many Human Genes Do All Current Drugs Target?

1) ~500 (2.5% of your genome)
2) ~1,000 (5%)
3) ~5,000 (25%)
4) ~10,000 (50%)
5) ~15,000 (75%)
6) ~20,000 (100%)
Now, Here is an Opportunity!

1) ~500 (2.5% of your genome)
2) ~1,000 (5%)
3) ~5,000 (25%)
4) ~10,000 (50%)
5) ~15,000 (75%)
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Prematurity

- We do not know all of prematurity’s causes, which severely limits prevention strategies.
- We should identify all the causes – biological, environmental, social – of prematurity within the next ten years!
- And use that knowledge to fashion more effective prevention strategies.
Newborn Screening in the Genome Era

- We will soon have the capability of obtaining an individual’s entire genome sequence at birth for a reasonable cost.
- That is a potential (probable?) game changer.
And, There is So Much More

• Such as...

Children are the living messages we send to a time we will not see.
- NEIL POSTMAN
Nature vs. Nurture

- It’s neither, of course – it’s both
- We now have unparalleled tools to help define the interactions among genetic and environmental factors - Nature and Nurture
- And, to use such understanding to improve children’s health and lives
Which Brings Us to “Epigenetics”

- We now know that environmental factors actually modify our genome
- But, we are just beginning to understand how this occurs
- Childhood appears to be a key period for epigenetic phenomena
- What are the mechanisms of this and how could we harness them to improve health?
For the first time, research will provide broadly applicable information about a child’s risks for adult onset disease.

It will also provide early biomarkers (and, sometimes, evidence of early onset) in children of diseases traditionally thought of as adult onset.

It will give us opportunities in pediatrics to affect the development of adult-onset disease.
Risk Factors for Chronic Bronchitis in the Elderly: The Copenhagen City Heart Study

- Male gender = 1.1
- Previous smokers = 1.7
- Alcohol consumption >3 drinks a day = 1.8
- Frequent chest infections in childhood = 2.1
- Exposure to dust and fumes at work = 2.2
- Current smokers = 2.8

Sue’s Story in 2025

- Sue enters the world at 26 weeks gestation, one of only 200,000 U.S. children born prematurely in 2025
- She develops necrotizing enterocolitis (NEC)
- Analysis of Sue’s gut microbiome shows that it contains a bacterium atypical for a premature baby and which research has shown helps cause NEC
Sue’s Story in 2025

- A multi-hospital clinical trial has shown an entirely new class of medication is effective against this bacterium.
- Sue’s genome-based newborn screening shows that she is not among the 8% of premature infants likely to suffer serious side effects from this drug, so she receives it and her NEC is cured.
Sue’s Story in 2027...

- Sue’s genome-based newborn screening also shows that she has a genetic variant which interacts specifically with dog dander to cause asthma
- So, grandma is instructed to buy her a cat, not a dog, for her second birthday
- Illness thus prevented, Sue never develops asthma
Sue’s genome-based newborn screening also shows that she has variants in seven genes that, together, increase her risk of early heart attack fivefold.

Sue, her parents, and her health care team design a prevention program, including diet and exercise starting in early childhood, and, starting at age 18, medication precisely targeted to her genetic makeup.
2055: Sue Has A Family

- Thanks to a new non-hormonal contraceptive, Sue safely delays pregnancy until finishing graduate school in forestry (she wants to live near Aspen) at age 30.
- Due to her family history of prematurity, Sue’s pregnancy is followed closely; when weekly monitoring of her vaginal flora shows early signs of impending labor, she is given a probiotic that prevents early delivery.
During the pregnancy, non-invasive testing shows the fetus has a genetic variant that greatly elevates risk of developing severe autism.

Therefore, Sue avoids a specific environmental exposure that research has demonstrated interacts with this genetic variation to cause autism.
Sue’s Family Grows Up

- Sue’s son, George, is born healthy at 39 weeks gestation and never develops autism.
- In 2096, George is elected the 60th President of the United States.
- In 2097, George doubles federal spending on child health research.
At age 75, Sue develops left arm pain that she assumes is due to gardening, but her primary care provider knows her higher risk and diagnoses an acute heart attack.

The drugs to treat her are selected based on her genome sequence.

Sue survives and is alive and active well into the 22nd century and becomes a great-great-grandmother...
Summary

- We are at an historic moment in pediatric research and care
- We have unparalleled opportunities to advance knowledge and to improve children’s health and well-being
- It is our privilege - and our responsibility to our children (and their children) - to invest in these opportunities
Thank You

• For what you are doing to make this better future a reality for our children and grandchildren