National University Hospital
Molecular Diagnosis Centre

Precision Medicine in Singapore - Perspective from the Molecular Diagnosis Centre at NUH

Molecular Diagnosis Centre
Department of Laboratory Medicine
National University Hospital

Benedict Yan

NUHS
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RAPID DETECTION
MONITORING
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METAGENOMICS
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NONINVASIVE EXLUSION OF SEX-LINKED DISEASES
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  - Genetic diseases
  - Prenatal diagnostics

APPLICATIONS OF NEXT-GENERATION SEQUENCING

Towards precision medicine

Euan A. Ashley

Abstract | There is great potential for genome sequencing to enhance patient care through improved diagnostic sensitivity and more precise therapeutic targeting. To maximize this potential, genomics strategies that have been developed for genetic discovery — including DNA-sequencing technologies and analysis algorithms — need to be adapted to fit clinical needs. This will require the optimization of alignment algorithms, attention to quality-coverage metrics, tailored solutions for paralogous or low-complexity areas of the genome, and the adoption of consensus standards for variant calling and interpretation. Global sharing of this more accurate genotypic and phenotypic data will accelerate the determination of causality for novel genes or variants. Thus, a deeper understanding of disease will be realized that will allow its targeting with much greater therapeutic precision.

The sequencing of the human genome led many to speculate on the near-term potential for clinical medicine[1]. Understanding the genetic basis of disease was naturally expected to lead to better targeted therapies. Indeed, the steep decline in the cost of sequencing, pursuant to the invention of 'next-generation' technologies, facilitated the discovery of many more causative genes[2,3] and, more recently, application to individual patients, including several widely reported examples of genome-driven medical decision making[4–6]. Pilot studies explored the use of genomic information more broadly in patient care[7–9] and the US National Human Genome Research Institute (NHGRI) laid out a 20-year plan for translating insights from genomics to medicine[10,11]. Additionally, direct-to-consumer companies put genotypes in the hands of interested participants[12]. However, the brightest spotlight was provided in 2015 by President Obama in his State of the Union address where he laid out a vision for a national Precision Medicine Initiative in the United States[13,14].

The term 'precision medicine' (BOX 1) was first given prominence by a publication from the US National Research Council that sought to inspire a new taxonomy for disease classification via a knowledge network[15]. In the appendix of that publication, the authors clarify that its coining, as opposed to the more commonly used term 'personalized medicine', was intended to convey the principle that although therapeutics were rarely developed for single individuals, increasingly, subgroups of patients could be defined, often by genomics, and targeted in more specific ways. Worldwide internet searches for the term increased dramatically after the State of the Union address and have remained at similar levels to that of 'personalized medicine' ever since (FIG. 1a).

The timing does seem right for a new approach: genomic data are more readily available, we have a greater understanding of population-scale genetic variation[16,17], and approaches to data integration with electronic medical records will lead to much improved characterization of phenotypes[18]. However, for precision medicine to succeed it also needs to be more accurate. The current algorithms for genome analysis were developed for population or cohort variant discovery where the consequences of reduced accuracy are a lost opportunity for discovery. By contrast, an inaccurate clinical genetic test could lead to very serious consequences for individuals and families with genetic disease. In this Review, I describe promising applications of precision medicine as it currently exists then move on to discuss the challenges our community needs to face, in the areas of sequencing technology, algorithm development and data sharing, to bring genomics up to clinical grade.

Promising applications of precision medicine

Cystic fibrosis. In the State of the Union address, President Obama specifically gave as an example the drug ivacaftor, which was developed for patients with cystic fibrosis. Cystic fibrosis is an autosomal recessive disease that affects approximately 70,000 people worldwide and that is caused by variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The protein product of this gene is an epithelial ion channel located on the cell surface where it regulates cellular chloride transit. Mutations of *CFTR* cause abnormal regulation of salt and water, which particularly affects the function of the lungs, pancreas and sweat glands. Recurrent pulmonary disease and resistant infection represent the major therapeutic challenges of cystic fibrosis, and traditional therapies have focused entirely

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GRAND round

NUH National University Hospital

Towards Precision Medicine

Speaker:

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Director, Stanford Center for Inherited Cardiovascular Disease
Director, Stanford Clinical Genomics Program
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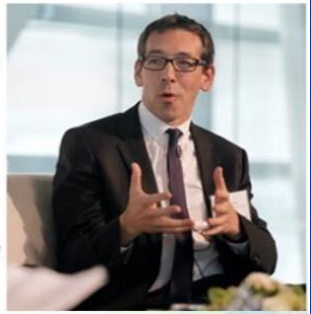


Chairperson:

A/Prof Roger Foo
Associate Professor of Medicine, Yong Loo Lin School of Medicine, National University of Singapore
Senior Consultant, Cardiac Department, National University Heart Centre
Senior Investigator, Genome Institute of Singapore (GIS)

Dr Benedict Yan
Head of Molecular Diagnosis Centre, NUH

Synopsis

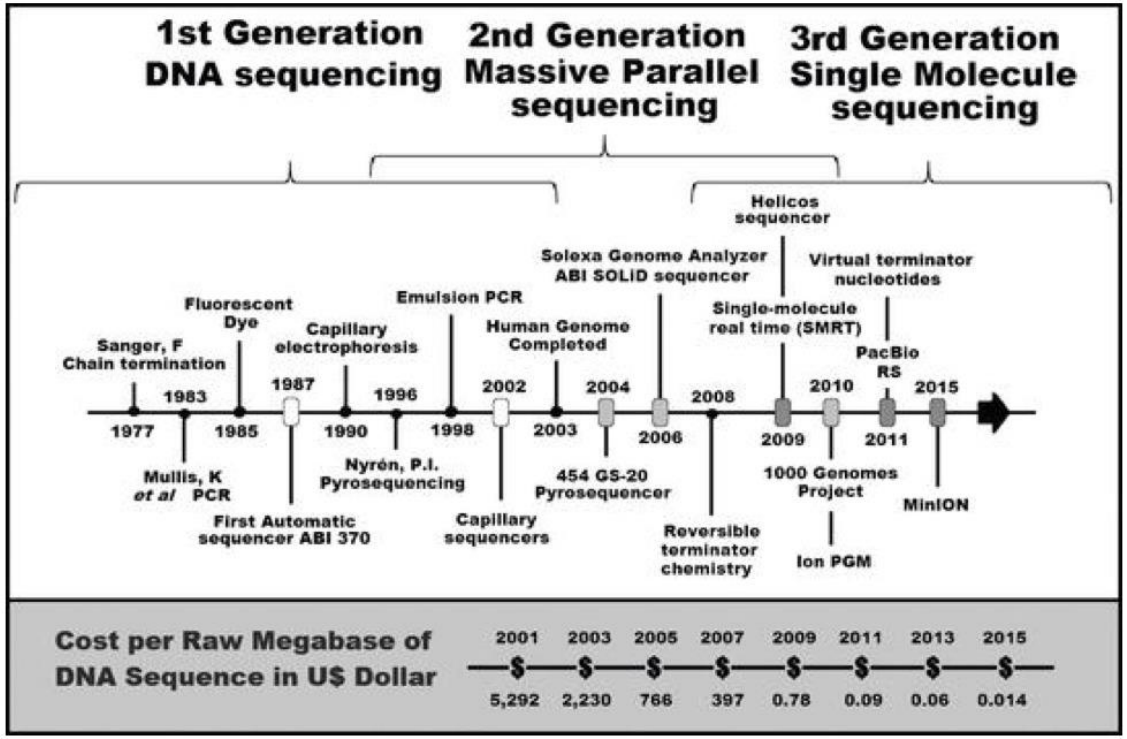
Fuelled by technological advancement, the past decade has witnessed a rapid acceleration in our understanding of the genetic basis of many diseases. With this greater understanding comes the possibility of redefining disease at a deeper level and targeting it with more precise therapy. In this talk, the speaker will discuss the history of the Precision Medicine concept and, using illustrative examples, outline the impact of genome sequencing on the management of patients with both rare and common diseases.

Date : 2 February 2018, Friday
Time : Registration & Breakfast at 7.10am – Talk begins at 7.40am
Location : NUHS Tower Block Auditorium, Level 1
Contact : Ms Sheri Tan, Tel: 6772 5992 | Email : sheri_xl_tan@nuhs.edu.sg

A member of the NUHS

The term 'precision medicine' (BOX 1) was first given prominence by a publication from the US National Research Council that sought to inspire a new taxonomy for disease classification via a knowledge network[15]. In the appendix of that publication, the authors clarify that its coining, as opposed to the more commonly used term 'personalized medicine', was intended to convey the principle that although therapeutics were rarely developed for single individuals, increasingly, subgroups of patients could be defined, often by genomics, and targeted in more specific ways. Worldwide internet searches for the term increased dramatically after the State of the Union address and have remained at similar levels to that of 'personalized medicine' ever since (FIG. 1a).

Evolution of sequencing technologies



Adopted from Pereira MA et al. (2017). Application of Next-Generation Sequencing in the Era of Precision Medicine In Marchi FA, Cirillo PD & Mateo EC (Eds), Biochemistry, Genetics and Molecular Biology - "Applications of RNA-Seq and Omics Strategies - From Microorganisms to Human Health". InTechOpen.

Courtesy of Dr Lee Hongkai

Clinical Genomics in Singapore - Current Landscape

- Oncology
  - Mostly small (<100 genes) targeted NGS panels
  - Larger panels cost-prohibitive
- Inherited Diseases
  - Cancer predisposition targeted panel
  - Whole-exome sequencing on the horizon (SureKids)
- Infectious Diseases
  - Metagenomics on the horizon
- Prenatal Diagnostics
  - NGS-based NIPT offered locally (iGene)

Challenges

- Skilled workforce:
  - Life science and medical graduates do not possess adequate genomic and computing literacy
  - Bioinformaticians scarce
  - Less than ten genetic counsellors on the island
- Organizational buy-in:
  - Management
  - Human resource
  - IT department

Infectious Diseases:
Metagenomics

Ministry of Health › Publications › Reports › 2016 › Communicable Diseases Surveillance in Singapore 2015

Communicable Diseases Surveillance in Singapore 2015

11 Nov 2016

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FOREWORD

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I am pleased to present the Ministry of Health's "Communicable Diseases Surveillance in Singapore 2015" Annual Report.

In 2015, we continued to face communicable diseases threats from around the world. The Middle East Respiratory Syndrome (MERS) outbreak in the Middle East continued, with a cumulative total of 1627 laboratory-confirmed cases, including 586 deaths, from 2012 to 2015. The risk of spread from a single imported case was highlighted when the Republic of Korea had a large outbreak, resulting in 186 cases, including 36 deaths, between May to July 2015. The outbreak of Ebola in Guinea, Liberia and Sierra Leone which started in 2014 resulted in 28,601 cases with 11,300 deaths (from 2014 to 3 January 2016). While the outbreak started to abate in early 2015, the three West African countries remain at high risk of additional small outbreaks. These incidents illustrated the importance of maintaining vigilance and being well prepared against different communicable diseases in an increasingly globalised and interconnected world.

SEVERE ILLNESS AND DEATH FROM POSSIBLY INFECTIOUS CAUSES (SIDPIC) PROGRAMME

The SIDPIC programme is a hospital-based sentinel surveillance programme which reviews cases of unexplained deaths and critical illness to identify possible emerging infections caused by novel pathogens. It aims to reduce delays in recognising emerging infections of public health importance. The project is presently operational in four public hospitals (TTSH, NUH, SGH and KKH). In year 2015, a total of 12,406 hospital patients were screened by SIDPIC project coordinators in participating hospitals (Table 1.30). Of these, 217 SIDPIC cases that fulfilled the inclusion criteria were identified. The majority of SIDPIC cases (35.48%) had illnesses with respiratory syndromes (Table 1.31). Of the 217 cases identified in 2015, 108 were found to have alternate aetiologies. 47 of these 108 cases had causative pathogens found. The top two causative pathogens were respiratory viruses (17%), and Streptococcus (17%). The remaining cases had clinical presentations that were consistent with the clinical diagnosis, e.g. auto-immune disorders. Despite extensive laboratory testing, the aetiology in 109 (50.23%) cases remained unknown. Table 1.32 lists the pathogens which may be tested for under the SIDPIC programme.

Accessed 9th March 2018

Source code:

Putting metagenomics to the test in the clinic

By Carrie Arnold

By July 2013, pediatrician James Gern had diagnosed hundreds of children at the University of Wisconsin Hospital in Madison, with ailments ranging from prosaic infections such as strep throat to emerging diseases such as West Nile virus. But one patient, a 14-year-old boy with an inherited immunodeficiency condition, who had been in the hospital for 32 days with encephalitis, stumped him. Three months before, the boy had complained of headaches and fever, which prompted a visit to Gern and a prescription of a steroid (prednisone) to reduce swelling, as well as an antibiotic (ciprofloxacin). But his condition continued to deteriorate. After intense seizures began wracking his thin frame, he was hospitalized. A brain biopsy failed to reveal a cause, and doctors placed the boy in a medically induced coma to halt the unrelenting and intensifying seizures.

"If we didn't figure out what was wrong and get him treatment, I knew his infection would likely be fatal," Gern says.

Gern contacted his collaborators Joseph DeRisi and Charles Chiu, microbiologists at the University of California, San Francisco (UCSF), to tap into their expertise. DeRisi and Chiu had been waiting for this type of phone call. They had developed a new platform that could be used for infectious diseases that defied diagnosis with standard protocols—perfect for Gern's patient. Instead of testing a sample of cerebrospinal fluid for one or two pathogens at a time, as Gern had been doing, the UCSF team used a technique called metagenomics to sequence all of the DNA in Gern's sample in one go. Software called sequence-based ultra-rapid pathogen identification (SURPI) analyzed the results and compared the DNA sequences in the sample to those found in publicly available genome databases. Within 48 hours, the UCSF platform, termed Precision Diagnosis of Acute Infectious Diseases, discovered the causative organism: a bacterium called *Leptospira santarosai*, which the patient had acquired on a trip to Puerto Rico the year before[1].

"We hadn't thought to look for *Leptospira*," Gern says, "but as soon as we started high-dose penicillin, he rapidly improved."

Over the past decade, metagenomics has freed microbiologists from the time- and labor-intensive need to culture organisms in a dish to identify them. The technique has opened new doors on efforts to catalogue and study microbes in the soil, air and water, giving scientists the ability to study prokaryotes that won't grow in the lab. It has also paved the way for the Human Microbiome Project and other efforts to map the range of commensal microbes growing in and on our bodies.

In the past few years, however, a small group of scientists has pioneered the use of metagenomics for the diagnosis of infectious disease. In March, Chiu and his team at UCSF launched a major clinical trial of a metagenomics diagnostic test for encephalitis and meningitis, which they say will forever change infectious-

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REVIEW

Encephalitis diagnosis using metagenomics: application of next generation sequencing for undiagnosed cases

Julianne R. Brown [a,*], Tehmina Bharucha [b,c], Judith Breuer [a,c]

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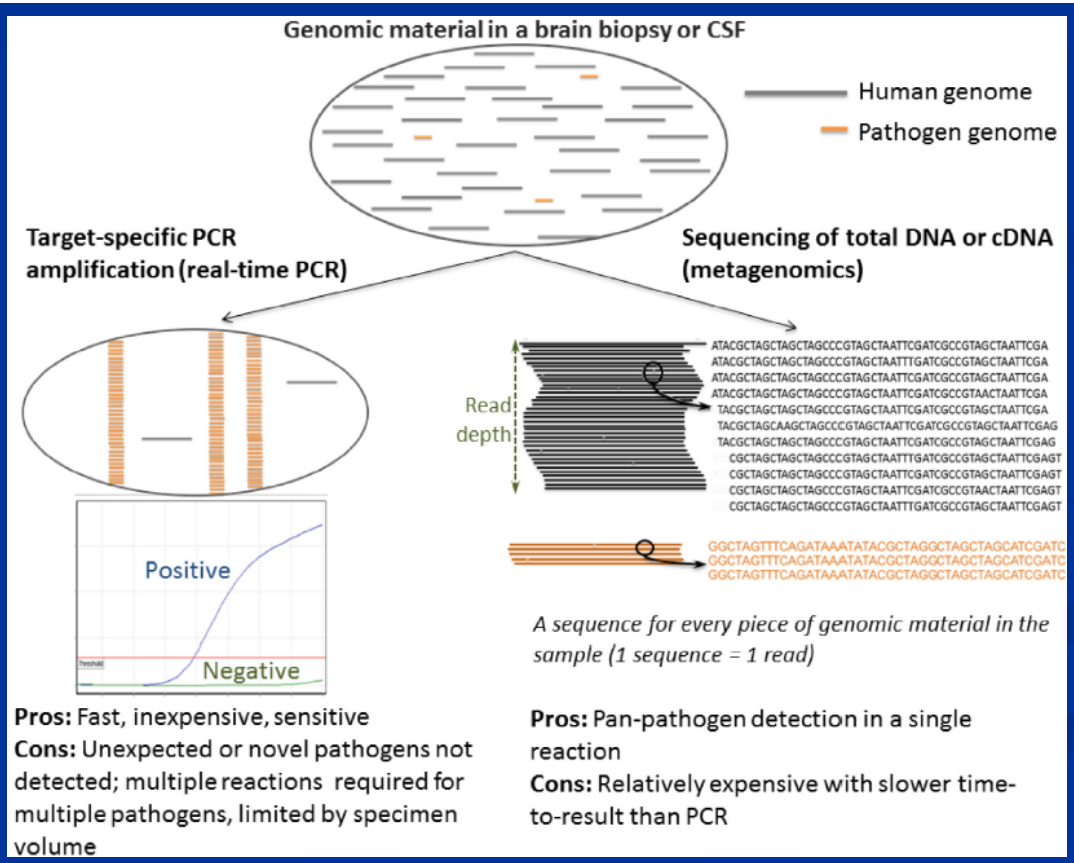
[b] Infectious Diseases and Microbiology, Royal Free London NHS Foundation Trust, UK
[c] Division of Infection and Immunity, University College London, UK



BRIEF REPORT

Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing

Michael R. Wilson, M.D., Samia N. Naccache, Ph.D., Erik Samayoa, B.S., C.L.S., Mark Biagtan, M.D., Hiba Bashir, M.D., Guixia Yu, B.S., Shahriar M. Salamat, M.D., Ph.D., Sneha Somasekar, B.S., Scot Federman, B.A., Steve Miller, M.D., Ph.D., Robert Sokolic, M.D., Elizabeth Garabedian, R.N., M.S.L.S., Fabio Candotti, M.D., Rebecca H. Buckley, M.D., Kurt D. Reed, M.D., Teresa L. Meyer, R.N., M.S., Christine M. Seroogy, M.D., Renee Galloway, M.P.H., Sheryl L. Henderson, M.D., Ph.D., James E. Gern, M.D., Joseph L. DeRisi, Ph.D., and Charles Y. Chiu, M.D., Ph.D.

From the Departments of Biochemistry and Biophysics (M.R.W., J.L.D.), Neurology (M.R.W.), and Laboratory Medicine (S.N.N., E.S., G.Y., S.S., S.F., S.M., C.Y.C.), and the Department of Medicine, Division of Infectious Diseases (C.Y.C.), University of California, San Francisco (UCSF), and UCSF–Abbott Viral Diagnostics and Discovery Center (S.N.N., E.S., G.Y., S.S., S.F., S.M., C.Y.C.) — both in San Francisco; the Department of Medicine, Division of Allergy and Immunology (M.B., H.B., J.E.G.), and the Departments of Pathology and Laboratory Medicine (S.M.S., K.D.R.) and Pediatrics (T.L.M., C.M.S., S.L.H., J.E.G.), University of Wisconsin, Madison; the Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD (R.S., E.G., F.C.); the Departments of Pediatrics and Immunology, Division of Allergy and Immunology, Duke University, Durham, NC (R.H.B.); and the Centers for Disease Control and Prevention, Atlanta (R.G.). Address reprint requests to Dr. Chiu at the Department of Laboratory Medicine, University of California, San Francisco, 185 Berry St., Box 134, San Francisco, CA 94107, or at charles.chiu@ucsf.edu.

This article was published on June 4, 2014, at NEJM.org.

N Engl J Med 2014;370:2408-17.
DOI: 10.1056/NEJMoa1401268

SUMMARY

A 14-year-old boy with severe combined immunodeficiency presented three times to a medical facility over a period of 4 months with fever and headache that progressed to hydrocephalus and status epilepticus necessitating a medically induced coma. Diagnostic workup including brain biopsy was unrevealing. Unbiased next-generation sequencing of the cerebrospinal fluid identified 475 of 3,063,784 sequence reads (0.016%) corresponding to leptospira infection. Clinical assays for leptospirosis were negative. Targeted antimicrobial agents were administered, and the patient was discharged home 32 days later with a status close to his premorbid condition. Polymerase-chain-reaction (PCR) and serologic testing at the Centers for Disease Control and Prevention (CDC) subsequently confirmed evidence of *Leptospira santarosai* infection.

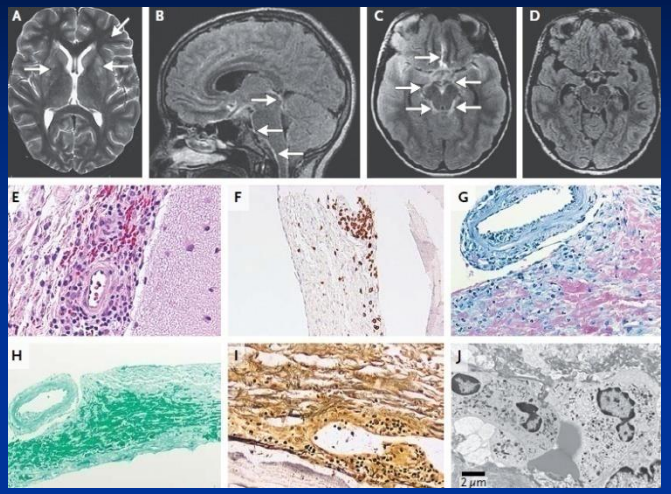
More than half the cases of meningoencephalitis remain undiagnosed, despite extensive clinical laboratory testing.[1-4] Because more than 100 different infectious agents can cause encephalitis, establishing a diagnosis with the use of cultures, serologic tests, and pathogen-specific PCR assays can be difficult. Unbiased next-generation sequencing has the potential to revolutionize our ability to discover emerging pathogens, especially newly identified viruses.[5-8] However, the usefulness of next-generation sequencing for the diagnosis of infectious diseases in a clinically relevant timeframe is largely unexplored.[9] We used unbiased next-generation sequencing to identify a treatable, albeit rare, bacterial cause of meningoencephalitis. In this case, the results of next-generation sequencing contributed directly to a dramatic effect on the patient's care, resulting ultimately in a favorable outcome.

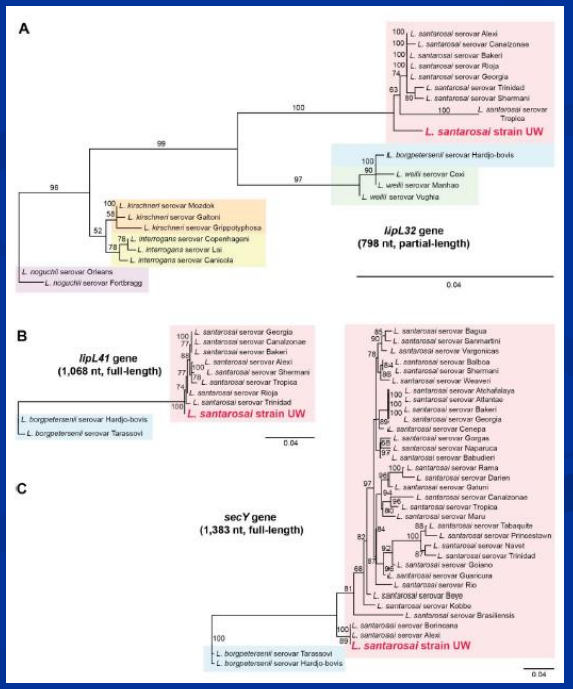
CASE REPORT

A 14-year-old boy with severe combined immunodeficiency (SCID) caused by adenosine deaminase deficiency and partial immune reconstitution after he had undergone two haploidentical bone marrow transplantations initially presented to the emergency department in early April 2013 after having had headache and fevers, with temperatures up to 39.4°C, for 6 days (Fig. 1A). He was admitted to the hospi-

Summary

- 14 year old boy
- Severe combined immunodeficiency
- Fever, headache to status epilepticus over 4 months
- Conventional diagnostic workup negative
- NGS of CSF revealed leptospira
- Antimicrobials given
- Discharged after 32 days





CURRENT OPINION

Metagenomics in pediatrics: using a shotgun approach to diagnose infections

2018

Jeffrey M. Bender[a,b] *and Jennifer Dien Bard*[b,c]

Purpose of review
With the advent of novel massively parallel sequencing technologies and bioinformatic processing capabilities, clinical applications of metagenomic studies are rapidly being integrated into medicine. Through this paper, we hope to introduce this powerful new tool to clinicians caring for children.

Recent findings
Very few studies have looked at metagenomic applications in children. The ability to perform these types of massive sequencing projects was not possible as little as 7 years ago.

Summary
Metagenomics is defined as the study of all genetic material within a given sample. Novel sequencing and analysis approaches allow for unbiased assays to identify pathogens missed by targeted sequencing and culture methods. Although not widely available yet, metagenomic studies have been used to diagnose pediatric infections, identify resistance genes in clinical samples, and characterize outbreaks. Although cost and turnaround time have limited its application in clinical laboratories to date, novel platforms and increasing comfort with these techniques continue to push diagnostic metagenomics into clinical pediatric medicine. Much work in this field is yet to be done. That being said, we feel that pediatric clinicians will be using metagenomic techniques in the care of children with increasing frequency in the near future.

Keywords
infectious disease, metagenomics, outbreak, resistance genes, shotgun sequencing

Journal of the Pediatric Infectious Diseases Society 2017

BRIEF REPORT

Neurobrucellosis: Unexpected Answer From Metagenomic Next-Generation Sequencing

Kanokporn Mongkolrattanothai[1,a], Samia N. Naccache[2,3,5,a], Jeffrey M. Bender[1], Erik Samayoa[3,5], Elizabeth Pham[3,5], Guixia Yu[3,5], Jennifer Dien Bard[2], Steve Miller[3,5], Grace Aldrovandi[1,6], and Charles Y. Chiu[3-5]

Metagenomic Analysis Identified Human Rhinovirus B91 Infection in an Adult Suffering from Severe Pneumonia

2017

To the Editor:

The clinical role of human rhinoviruses (HRVs), the common respiratory viruses, in lower respiratory tract infections has been long questioned because of their high frequency in asymptomatic people (1). Recent studies strongly suggest the importance of HRVs in the pathogenesis of severe community-acquired pneumonia (SCAP) (2, 3). Here, we identified a rarely reported HRV-B91 infection in a patient with SCAP, using metagenomic analysis. Some of the results of this study have been previously reported in the form of an abstract (4).

A 60-year-old woman was admitted in October 2015 because she had had a fever for 3 days (maximum temperature, 39°C), chills, cough, and worsened dyspnea without previously recorded medical issues. She was diagnosed with SCAP, and her general condition progressively worsened. Chest computed tomography showed patchy consolidation in the right lower lobe on Day 1 and then bilateral alveolar consolidation on Day 3 after the onset of symptoms. Her white blood cell count increased from 2.4×10^9/L

Clinical Metagenomics for the Diagnosis of Hospital-acquired Infections: Promises and Hurdles

2017

To the Editor:

We read with interest the paper by Pendleton and colleagues (1) [this issue, pp. 1610–1612] about the rapid identification of respiratory bacterial pathogens directly from a mini–bronchoalveolar lavage sample using the MinION sequencer (Oxford Nanopore Technologies, Oxford, UK). Within hours of the samples being

Journal of the Pediatric Infectious Diseases Society 2017

ORIGINAL ARTICLE

Rule-Out Outbreak: 24-Hour Metagenomic Next-Generation Sequencing for Characterizing Respiratory Virus Source for Infection Prevention

Alexander L. Greninger,[1,2] Alpana Waghmare,[2,3] Amanda Adler,[3] Xuan Qin,[1] Janet L. Crowley,[1] Janet A. Englund,[3] Jane M. Kuypers,[1] Keith R. Jerome,[1,2] and Danielle M. Zerr[2,3]

Metagenomic Sequencing Detects Respiratory Pathogens in Hematopoietic Cellular Transplant Patients

2018

To the Editor:

Lower respiratory tract infections (LRTIs) are a leading reason for hospitalization and mortality in hematopoietic cellular transplant (HCT) recipients (1). Despite this, the etiologic

Rapid Pathogen Identification in Bacterial Pneumonia Using Real-Time Metagenomics

2017

To the Editor:

Pneumonia remains a tremendous cause of morbidity, mortality, and healthcare expense (1). Despite the recent revolution in culture-independent microbiology (2), clinical identification of respiratory pathogens still relies on the culture-based techniques used by Pasteur in the 1880s (3). Delayed identification of pathogens in pneumonia can result in increased morbidity and mortality, as well as indiscriminate use of broad empiric antibiotics, impeding antimicrobial stewardship. Although novel sequencing-

Clinical Chemistry 61:1
25–31 (2015)

Reflections

Nanopore Sequencing: From Imagination to Reality

Hagan Bayley[1*]

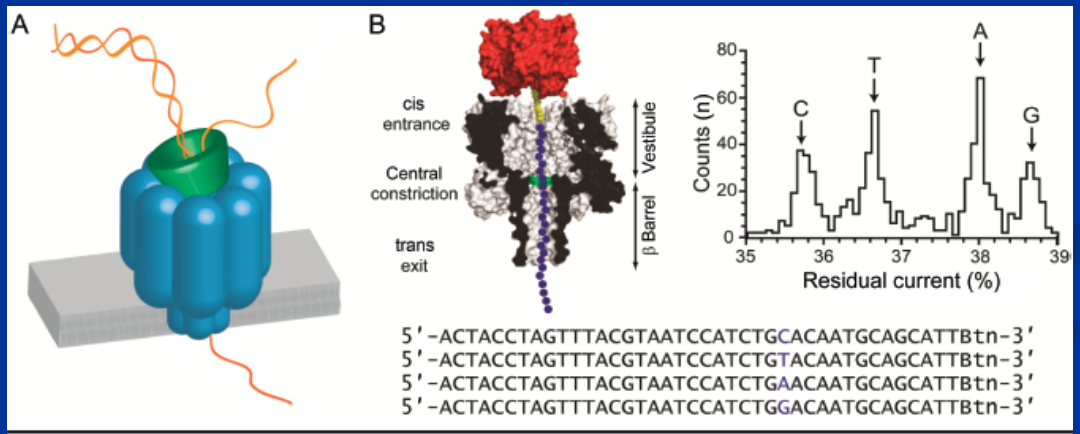
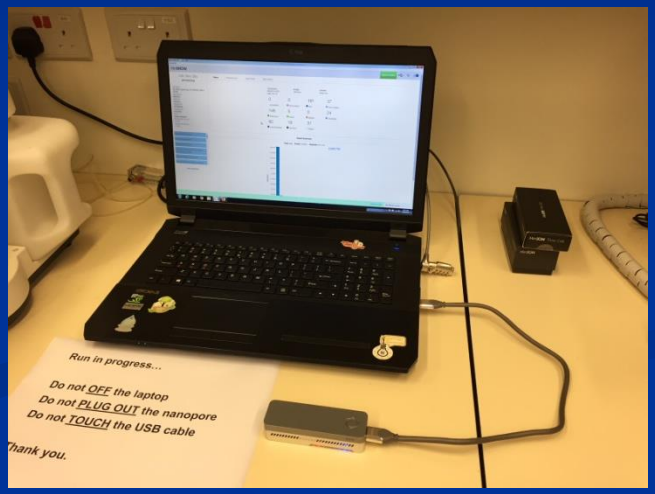


Fig. 2. Nanopore strand sequencing.

(A), Basis of nanopore sequencing. ssDNA is fed through an individual protein pore by an enzyme that handles dsDNA. The sequence is determined by analysis of fluctuations in the ionic current. (B), Early base identification experiments. ssDNAs were suspended in an αHL pore by attachment to streptavidin to mimic the ratcheting motion of the enzyme. The bases G, A, T, and C in a DNA hetero-oligomer each gave a different residual ionic current. Adapted with permission from Stoddart et al. *(25)*.



Dr Gabriel Yan, Lee Chun Kiat

SINGAPORE MOLECULAR DIAGNOSTICS SYMPOSIUM 2018

GENOMICS IN HEALTHCARE

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All fees are inclusive of 7% GST

REGISTER DISCOVER

MATTHEW BINNICKER
(NGS for Infectious Diseases)
Mayo Clinic, Rochester, Minnesota
ABSTRACT

RAYMOND CHUA
(Regulation of Genomic Testing in Singapore)
Regulatory Compliance and Enforcement Div, MOH
ABSTRACT

ALLEN YEOH
(Genomics of Acute Lymphoblastic Leukemia)
Department of Paediatric Haematology-Oncology, NUS
ABSTRACT

GLENN FRANCIS
(Cancer Genomics)
Genomics For Life, Australia
ABSTRACT

HO-WAN IP
(Genomics of Hematolymphoid Malignancies)
Queen Mary Hospital, Hong Kong
ABSTRACT

KAREN TAN
(Quality in Genomics)
Molecular Diagnosis Centre, National University Hospital
ABSTRACT

KENNETH BAN
(Genomic Education)
Biochemistry, NUS
ABSTRACT

KUAN WIN SEN
(Genomics of Sepsis)
Yong Loo Lin School of Medicine, NUS
ABSTRACT

LAW HAI YANG
(Thalassemia)
KK Women's and Children's Hospital
ABSTRACT

LAI POH SAN
(Clinical NGS Diagnostics)
Department of Paediatrics, NUS
ABSTRACT

LIM SU CHI
(Precision Medicine in Diabetes)
Khoo Teck Puat Hospital
ABSTRACT

IAN CAMPBELL
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Peter MacCallum Cancer Centre, Victoria, Australia
ABSTRACT

OCTOBER SESSIONS
(Virology Genomics)
Emerging Infectious Diseases, Duke-NUS
ABSTRACT

OWEN SCHAEFER
(Ethics of Genomics Testing)
Centre for Biomedical Ethics, NUS
ABSTRACT

RICK ONG
(Microbial Genomics)
Saw Swee Hock School of Public Health, NUS
ABSTRACT

TAI E SHYONG
(Precision Medicine)
Saw Swee Hock School of Public Health, NUS
ABSTRACT

TOMMY LAM
(Viral Genomics)
School of Public Health, The University of Hong Kong
ABSTRACT

LOUIS CHAI
(Infectious Disease NGS)
Yong Loo Lin School of Medicine, NUS
ABSTRACT

Thank You

Our Team

Dr Karen Tan
Lily Chiu
Dr Lee Hong Kai
Lee Chun Kiat
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Mui Joo Khoo
Huan Pei Tee
Lee Peak Ling
Ng Sau Yoke
Alynn Ang
Leong Mun Han
Jenny Chai
Tracy Png
Bustamin Kosmo
Sharah Capinpin
Patrice Tan
Ng Li Jie