Mission Genomics into the Clinic
- Support molecular diagnostic devices
- Enable clinicians to deliver innovative therapies,
- Optimize care processes to improve a patient's health

Vision Koers 018 Personalized Health Care
- Educate, Develop and Support software solutions that allow collaborative multidisciplinary decisionmaking to deliver patient-centric value-based health care
- Introduce into the Clinic

Strategy Patient Stratification
- Molecular Diagnostics
- Targeted Treatment

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Personalized Medicine – what is it?

• ... to improve the efficacy of a drug

• ... to improve the safety of a drug

• ... to improve the dose regiment of a drug
Analytics are Vital to HC Transformation

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Diagnostic Sequencing in Rotterdam

Sophia
Genetics
Congenital malformation: 1/100

World Health Organization

Monogenic diseases are responsible for a heavy loss of life. The global prevalence of all single gene diseases at birth is approximately 10/1000. It has been estimated that taken together, monogenic diseases may account for up to 40% of the work of hospital-based pediatric practice.

Complete genomics
For Profit

Academic UMC Data Hubs
Non for Profit

Daniel
Pathology
Cancer: 1/4

World Health Organization

DNA sequencing provides insight on the causes of human cancer, the mechanisms of carcinogenesis, and helps to develop scientific strategies for cancer prevention and control. All cancers arise as a result of the acquisition of a series of fixed DNA sequence abnormalities, mutations, many of which ultimately confer a growth advantage upon the cells in which they have occurred.

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Impact of Genomics, Smart Diagnostics

4% of Health Cost spent on Dx

72% of decisions based on Dx
Data Visualization & Knowledge Integration

PCA Clusters
How is every record related to every other?

Heatmap
What is the range and distribution of values?

Chem. Structures
How are the Lipids/compounds distributed in the data?

Chromosomes
Where are the mutations/variants located?

Brain Atlas
What are the major themes or concepts?

Patient Correlation
How are the numeric attributes correlated?

Pathway Networks
What are the supported regulatory relationships?

DNA, RNA & Protein Sequence data
Ref: GACGACCATAGACCAGCAT
Allele1
GACGACCATAGACCAGCAT
GACTACCATAGACT-GCAA
Allele2
What is the underlying natural sequence variation?

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Innovative Diagnostic Tests

Low grade

High grade

- Neuropathology: Prof. dr. J.M. Kros -
- Visit Alabama delegation to Rotterdam: October 2014 -
Patient Stratification (Glioblastomas)

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Research ≠ Clinical Decision Support

Evidence & Licensed Reference Data

Translational Research

Molecular Diagnosis

Source Data Systems

Analytics Layer

Clinical Action

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Working With a Global Community

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Craniofacial Development

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Dramatically Different Economics

- Current tests: run chemistry for each test
  - $100s-$1,000s per test

- UGT: run chemistry only once per person
  - ~$1,000 one-time up-front cost
  - Marginal cost of future tests is nearly zero (cost of a database storage and lookup)
Comorbidity in Craniofacial Patients

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Malformations of the Skull

- Trigonocephaly
- Scaphocephaly
- Metopic Synostosis
- Sagittal Synostosis
- Unicoronal Synostosis
- Plagiocephaly
Human Syndromes

Cognitive impairment
Cochlea: hearing loss
Cerebellum
Craniofacial abnormalities

Thoracic skeleton
Lung and airway abnormalities
Liver cysts

Pancreatic cysts
Renal cysts
Sterility

Obesity
Polydactyly
Skeletal abnormalities

2011 EJHG Vol 19 D. Johnson & A. Wilkie

Nature Reviews Genetics May 2010

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Parallels between Patients & Animal Models

Nature Reviews Genetics May 2010

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Vertebrate Evolution

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Solidarity: Need for Reimbursed Diagnostic WGS

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Facial Development

Week 5
Week 6
Week 7
Week 8
Week 9
Week 10

FrontoNasal
Maxillary
Mandibular

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Measurement of Head Circumference

Prefrontal Cortex

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Molecular Genetics of Brain Development
Analyses of a set of 128 ancestry informative single-nucleotide polymorphisms in a global set of 119 population samples


Abstract

Background: Using DNA to determine an individual’s ancestry from among human populations is generally interesting and useful for many purposes, including admixture mapping, controlling for population structure in disease or trait association studies and forensic ancestry inference. However, to estimate ancestry, including possible admixture within an individual, as well as heterogeneity within a group of individuals, allele frequencies are necessary for what are believed to be the contributing populations. For this purpose, panels of ancestry informative markers (AIMs) have been developed.

Results: We are presenting our work on one such panel, composed of 128 ancestry informative single-nucleotide polymorphisms (AISNPs) already proposed in the literature. Compared to previous studies of these AISNPs, we have studied three times the number of individuals (4,871) in three times as many population samples (119). We have validated this panel for many ancestry assignment and admixture studies, especially those that were the rationale for the original selection of the 128 SNPs: African Americans and Mexican Americans. At the same time, the limitations of the panel for distinguishing ancestry and quantifying admixture among Eurasian populations are noted.

Conclusion: We demonstrate the simultaneous importance of the specific set of population samples and their relative sample sizes in the use of the structure program to determine which groups cluster together and consequently influence the ability of a marker panel to infer ancestry. We demonstrate the strengths and weaknesses of this particular panel of AISNPs in a global context.
Leukemia Patient Stratification

Dr. P. Valk, Prof. Dr. B. Löwenberg

Better Overall Survival & Event Free Survival

The NEW ENGLAND JOURNAL of MEDICINE

Low number of White Blood cells
TCGA Cancer Profiling Data @ EMC

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Mutations in Cancer & Development

- Neural Crest Stemcell Differentiation -

- Plastic Surgery: Prof dr SER Hovius & Prof dr I. Mathijssen -
Parallels between Development and Cancer

Same Pathways in Cancer & Development!

doi:10.1038/ng.2557, nature 2013

do 10.1016/j.cell.2011.08.017

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What Must Change to Allow Personalized Healthcare?

- Caregivers
- Payers
- Patients

Education

Reimbursement

Legislation

Regulation

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Conclusion

New opportunities for disease management

- Expression based classification of biological subgroups
- Identifying DNA variants relevant for Dx & therapy
- Companion diagnostics for directed therapy
- Assessing and managing risk

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Bioinformatics Team

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- Christine Troelstra
- Bas Horsman
- Sylvia de Does
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  - Steven Hovius
  - Irene Mathijssen
  - Jacqueline Goos

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