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Genetic Diagnostics – Challenges for the Future

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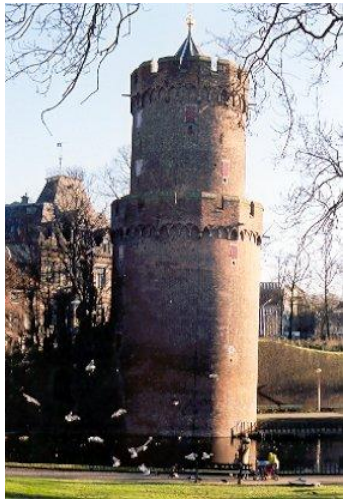
..TGATTCGGT

AATGACAGT..

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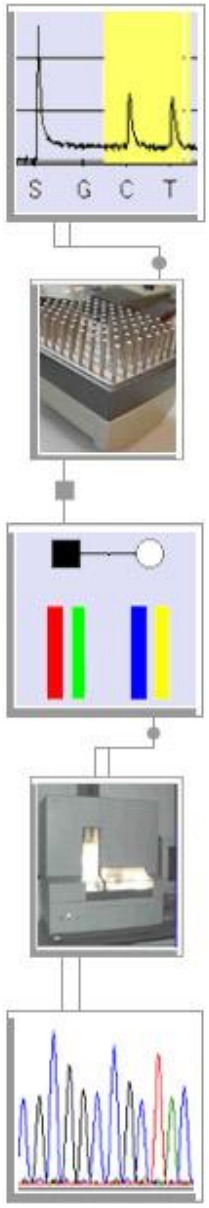
Challenges for the Future

- Service to Customers
- Quality assurance / Cost effectiveness
- Integration / Collaboration with other disciplines
- Multifactorial disease / Pharmacogenetics
- Technical Innovation
- Ethical considerations



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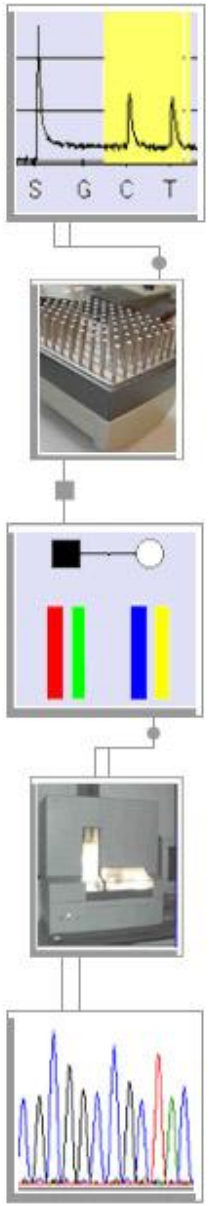
Challenges for the Future



➢ Service to Customers

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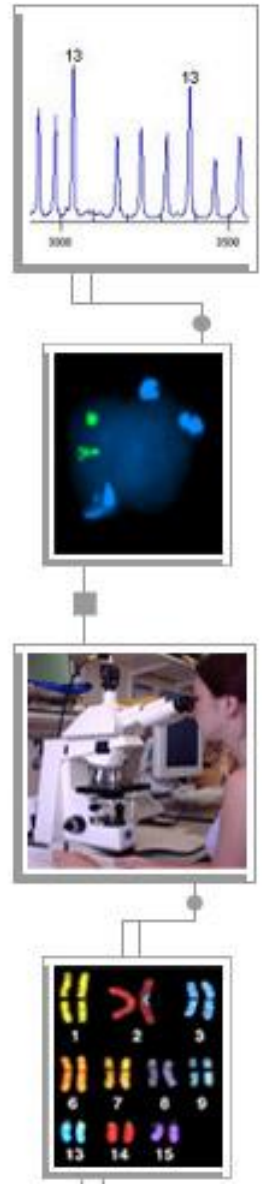
Service to Customers (1)

Turn Around Time (TAT)



"The Genetics White Paper"		
Prenatal diagnosis:	3 days	(2 weeks)
Known mutation:	2 weeks	(6-8 weeks)
Unknown mutation:	8 weeks	(3-6 months)

Strive for shorter TATs

Without compromizing quality assurance

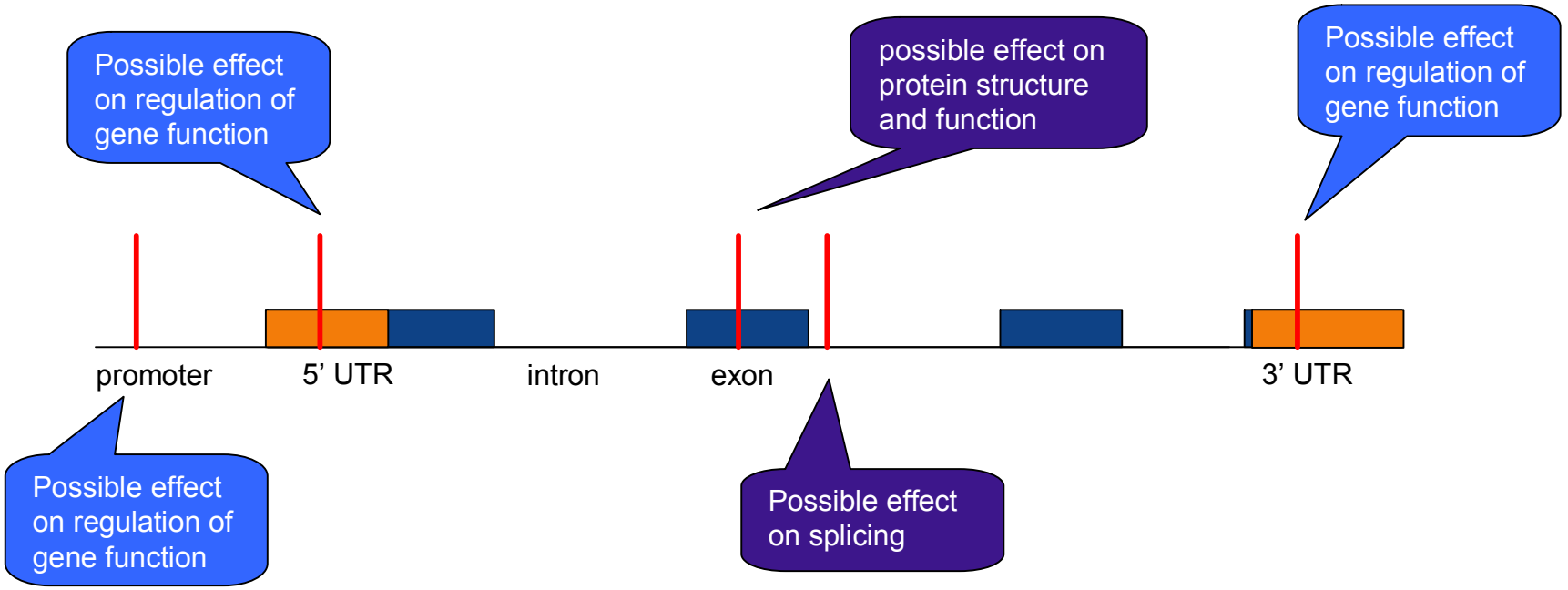
Take into consideration: workload, capacity, cost

How short is necessary?

TATs dependent on the clinical usefulness of test results

Service to Customers (2)

Increasing Test Sensitivity



- Mutations in non-coding regions
- Rearrangements (MLPA)
- Chromatin modulation

} Implications for TATs and cost

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Service to Customers (3)

Availability of Tests

OMIM	Total
# Phenotype description, molecular basis known	**1933**
% Mendelian phenotype or locus, molecular basis unknown	**1528**

3461 → **1500 genes**

Tests offered

~350 genes

~500 genes

Statistics on Hereditary Diseases (OMIM, July 11, 2006)

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Service to Customers (4)

Availability of Tests

- Based on OMIM statistics, we are not even half way
- Testing for rare disorders can not be offered by each laboratory
- Further (European) networks required

EuroGentest

orphanet

Commercial Laboratories, how to compete

- Quality assurance
- Role for Clinical Molecular Geneticist?
- Embedded in Clinical Genetics?
- Service, easy accessible

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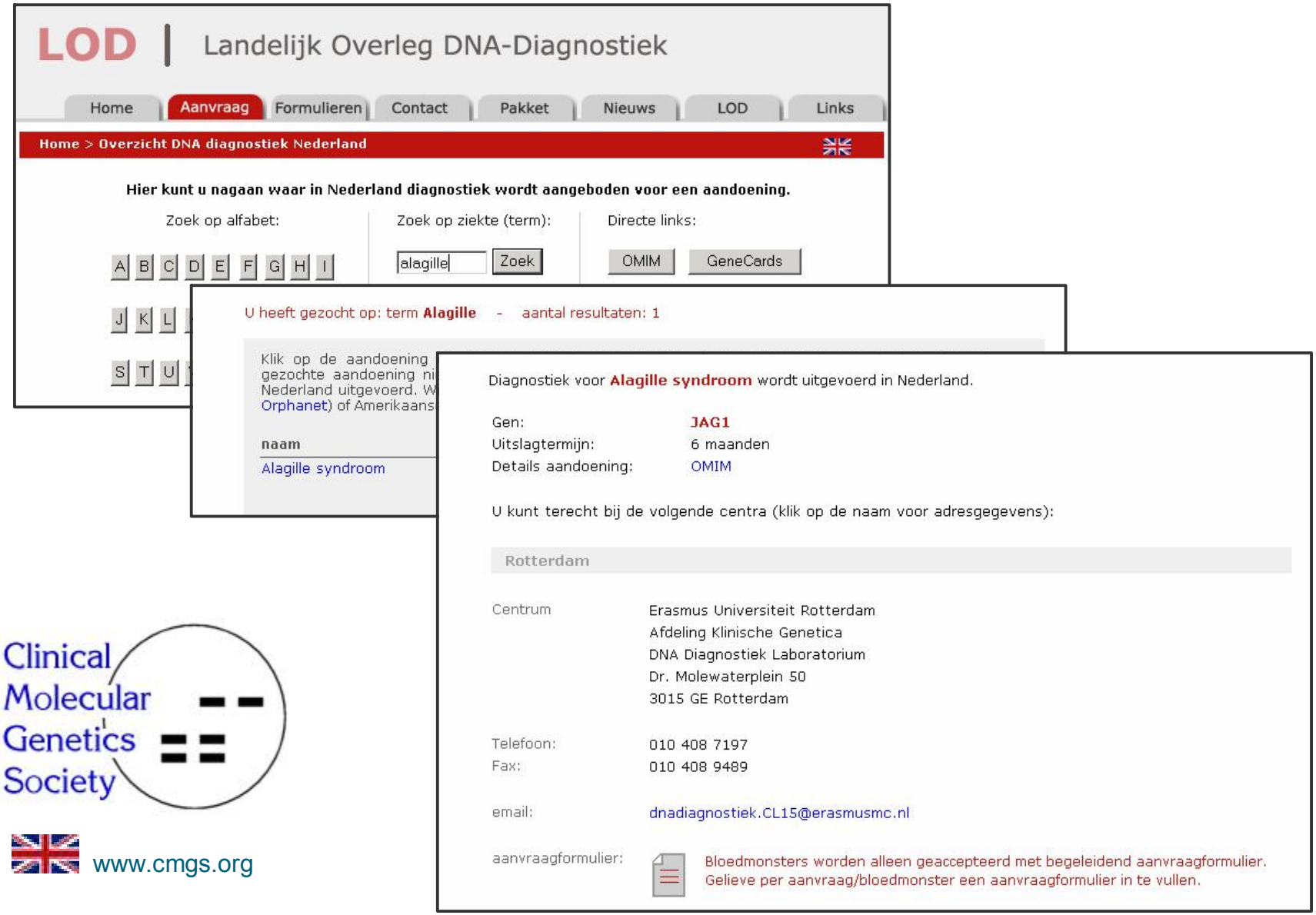

Clinical Molecular Genetics Society

www.cmgs.org

www.dnadiagnostiek.nl

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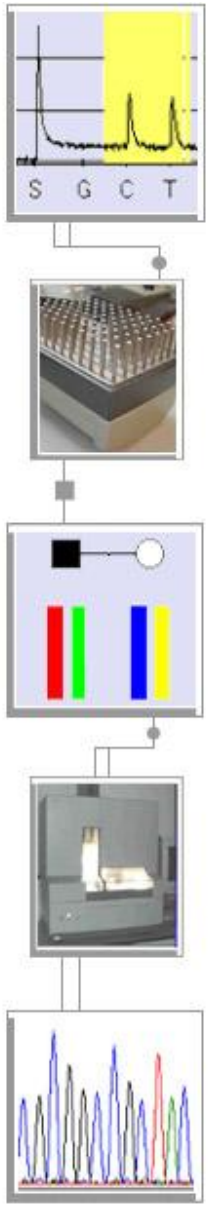

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Quality Management

Quality management plays a crucial role !

Instruments:

- Accreditation Programmes
- Best Practice Guidelines
- External Quality Assessment Schemes
- Development of Reference Materials
- Educational and Professional Registration Programmes for Scientific Lab Personnel, including regular site visits

UKNEQAS

EMQN

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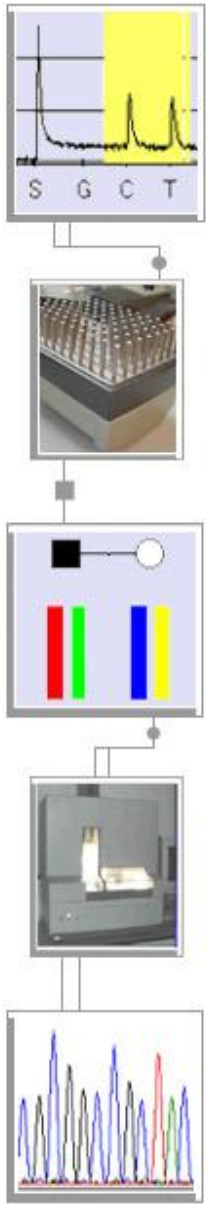
Cost Effectiveness



Cost reduction

- Automation
- Defining inclusion criteria

  e.g. subtelomeric rearrangement screening (MLPA)

  in mental retardation (Koolen et al 2004)

Disorders with extended locus heterogeneity

→ many potentially causative genes

e.g. hereditary blindness, hereditary deafness, Walker Warburg

Parallel mutation analysis → What is the best way to do this?

Dedicated SNP/mutation-array (e.g. APEX)

Resequencing approaches?

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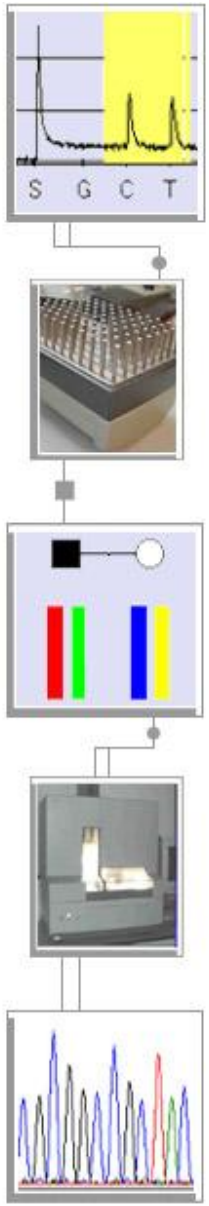

Collaboration / Integration

- Integration cytogenetics and molecular genetics

  array CGH

  SNP Array

  exon arrays (MLPA)

  → Will have consequences for training programs

- Integration genomics, proteomics, metabolomics

  Proteomics may be important for sub classification of genetic heterogenic diseases

  → Will reduce the number of required DNA tests

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Challenges for the Future

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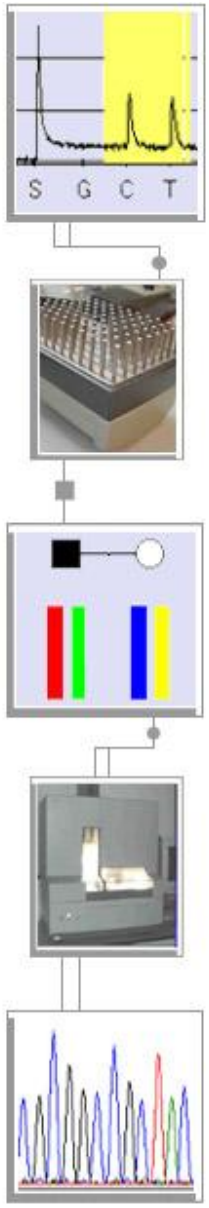

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Multifactorial Disease and Pharmacogenetics

Gen*	Genetische variant	Opmerkingen
CARD15 / NOD2	3020InsC, 2104C>T en 2722G>C	Risicofactor voor ziekte van Crohn
ADRB2	46A>G (Arg16Gly) en 79C>G (Gln27Glu)	Risicofactor voor verminderde respons op β2-adrenoceptor agonisten
CYP2C9	CYP2C9*2 en CYP2C9*3	Risicofactor voor vertraagd metabolisme van anticoagulantia, antipsychotica, etc. (zie lijst van CYP2C9 substraten onderaan)
CYP2C19	CYP2C19*2 en CYP2C19*3	Risicofactor voor vertraagd metabolisme van anticoagulantia, anticonvulsiva, antidepressiva, etc. (zie lijst van CYP2C19 substraten)
CYP2D6	CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6 en CYP2D6*2xn	Risicofactor voor vertraagd of versneld metabolisme van narcotica, cardiovasculaire middelen, etc (zie lijst van CYP2D6 substraten)
TPMT	TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, TPMT*3D, TPMT*4, TPMT*5, TPMT*6, TPMT*7 en TPMT*8	Risicofactor voor vertraagd metabolisme van thiopurines (gebruikt voor chemotherapie en immuunsuppressie)
Mitochondrieel DNA	1555A>G en DelT961	Risicofactor voor ototoxiciteit door aminoglycoside-gebaseerde antibiotica.
RYR1**	Mutatie analyse van 11 exonen waarin de meeste mutaties zijn beschreven.	Risicofactor voor Maligne Hyperthermie (ten tijde van algehele narcose).

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Multifactorial Disease and Pharmacogenetics

- Clinical (genetic) applications currently limited:

  Genetic risk factors ⟺ Environmental factors

  Testing will result in genetic risk, rather than providing definite diagnosis

- Will be mainly applied in treatment-related diagnostics
- Evidence base and cost effectiveness first required

Pharmacogenetics has not yet delivered on the expectations.
What are the implications?

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Challenges for the Future

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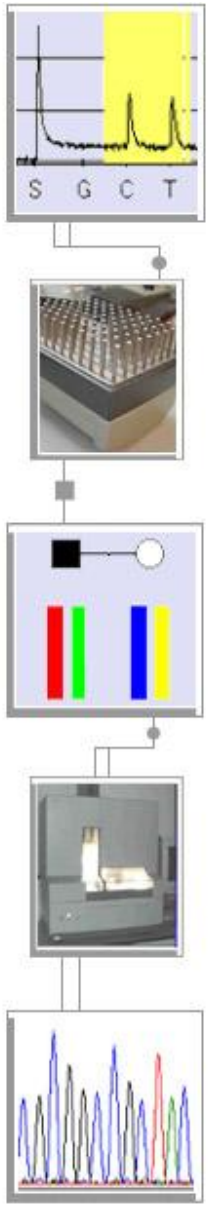
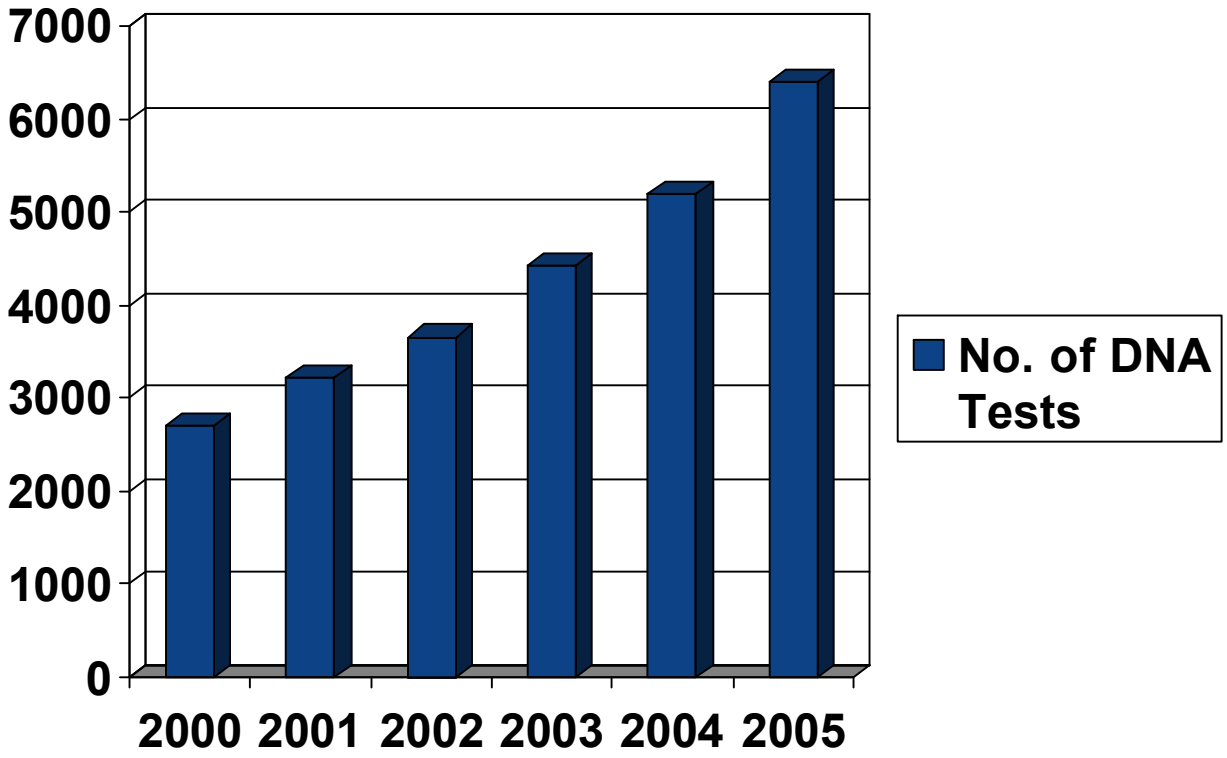


DNA tests Nijmegen 2000-2005



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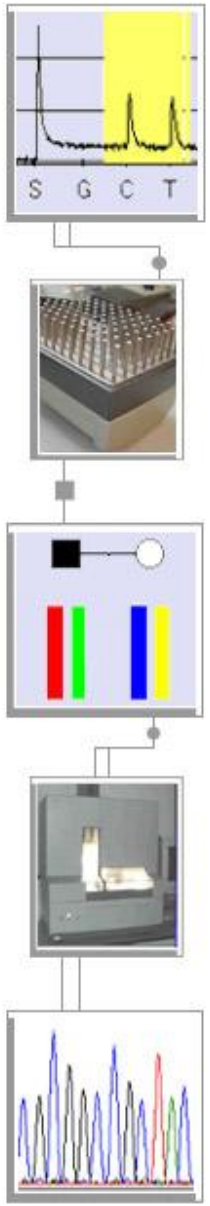
Technical Innovations in Genetics (1)



- For monogenic (and multifactorial) disorders robotisation / high throughput techniques are needed

  Cope with the growing demand for tests

  Relief workload

  Shorten TATs

  Reduce Cost

  Improve Quality Assurance

  (e.g. automated sample tracking)

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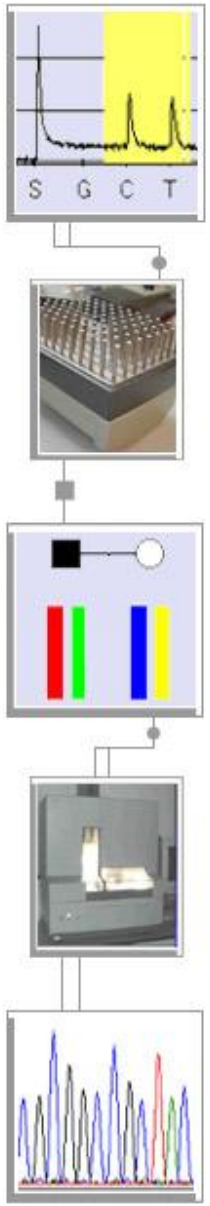
Technical Innovations in Genetics (2)



- Who determines the technological developments?

  Influence of expert geneticists is important

  e.g. Automated read-out systems

  could resolve current major bottleneck in efficient lab flow

- Where are we now, and where do we want to go?

  e.g. whole genome analysis vs. specific mutation detection

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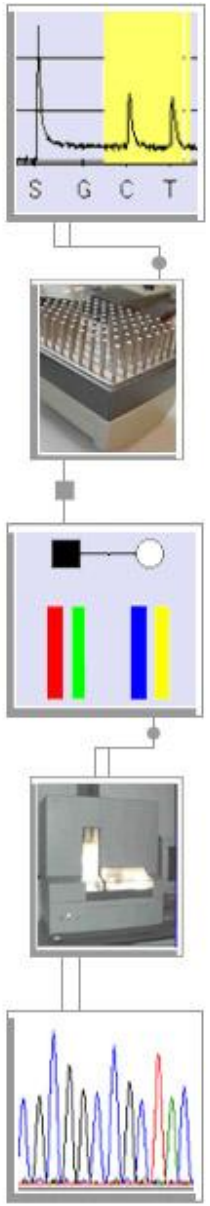
Technical Innovations in Genetics (3)



- Genetic experts should be involved in this innovative process

  - ➢ To warrant that the required software or hardware is being developed

  - ➢ To avoid the development of irrational test kits

→ e.g. combination of tests for different disorders

Examples of Inappropriate Test Kits

- CFTR mutation kit including test for 5T allele
  not relevant for CF: implications restricted to obstructive azoospermia (CBAVD)

- MLPA kit for numerical chromosomal aberrations including tests for microdeletion syndromes

- MLPA kit for numerical chromosomal aberrations including tests for congenital adrenal hyperplasia, or spinal muscular atrophy
  would also imply carrier detection of these relatively frequent autosomal recessive disorders

In general, specific testing for particular disease preferable over more generalized (whole genome) approaches

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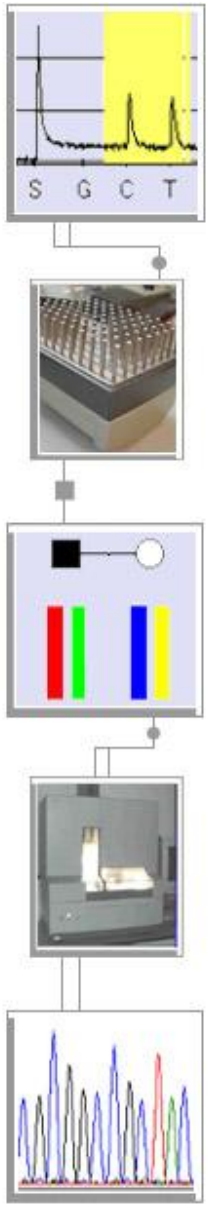
Technical Innovations in Genetics (4)



- Intellectual contribution of geneticists beneficial for commercial developers (novel ideas, tailor-made products)
- Genetic experts should be leading in this innovative process by being proactive!!

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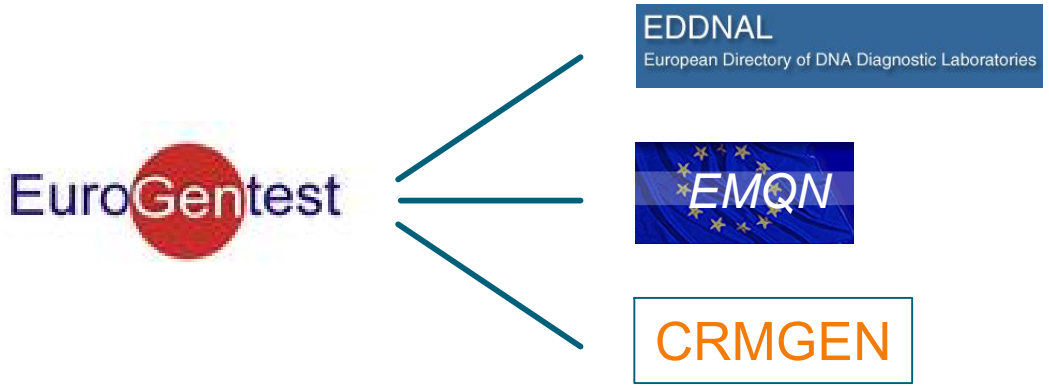
Technical Innovations in Genetics (5)

Strategy for Implementation

- EUROGENTEST plays a key role in the improvement of the quality assurance issues



- A technological innovation platform superimposed on EUROGENTEST could possibly resolve the innovation issues discussed

  → active role of genetic experts in innovation

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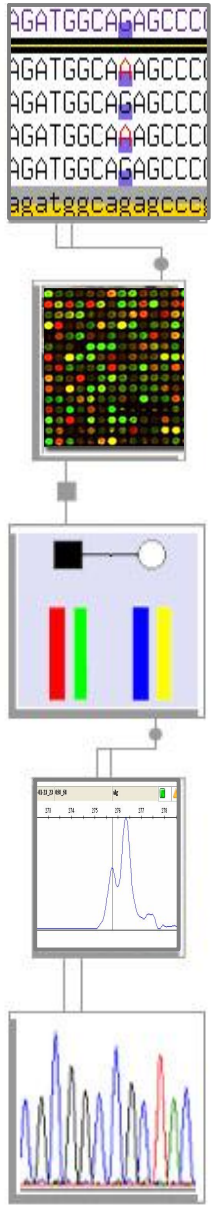
Technical Innovations in Genetics (6)
Data Interpretation



Novel mutation: is it deleterious?

- Sharing information
  - Publish findings
  - Comprehensive Mutation databases
  - → Submission of unpublished data

- Improving prediction algorithms

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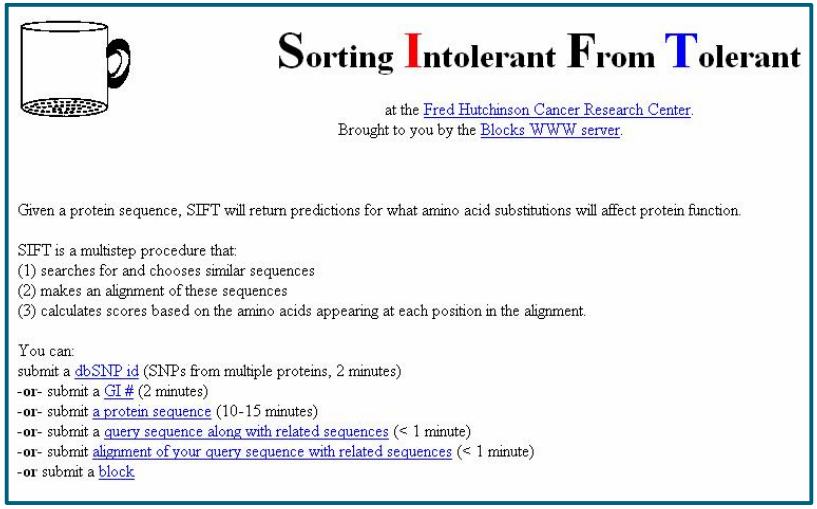
Deleterious Mutation Prediction Methods

Missense mutations

SIFT

Collects sequence homologues in multiple alignments and identifies non-conservative changes in amino acids



Sorting Intolerant From Tolerant

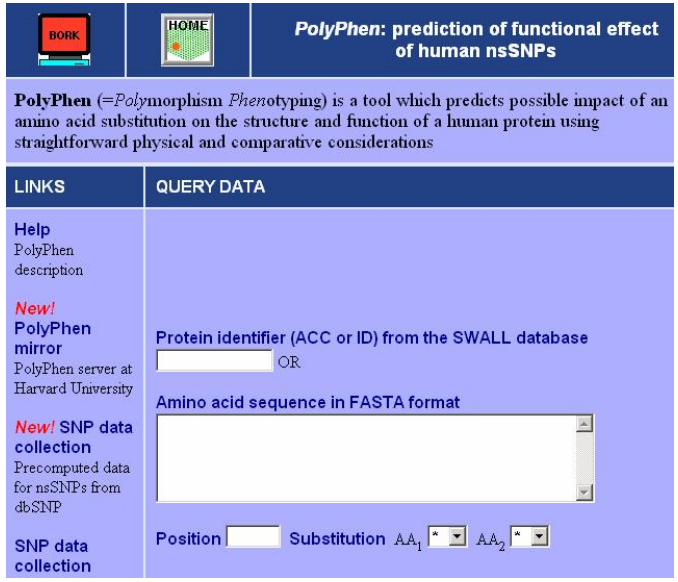
at the Fred Hutchinson Cancer Research Center.
Brought to you by the Blocks WWW server.

Given a protein sequence, SIFT will return predictions for what amino acid substitutions will affect protein function.

SIFT is a multistep procedure that:
(1) searches for and chooses similar sequences
(2) makes an alignment of these sequences
(3) calculates scores based on the amino acids appearing at each position in the alignment.

You can:
submit a dbSNP id (SNPs from multiple proteins, 2 minutes)
-or- submit a GI # (2 minutes)
-or- submit a protein sequence (10-15 minutes)
-or- submit a query sequence along with related sequences (< 1 minute)
-or- submit alignment of your query sequence with related sequences (< 1 minute)
-or submit a block

http://blocks.fhcrc.org/sift/SIFT.html



BORK | HOME | ***PolyPhen*: prediction of functional effect of human nsSNPs**

PolyPhen (=*Poly*morphism *Phen*otyping) is a tool which predicts possible impact of an amino acid substitution on the structure and function of a human protein using straightforward physical and comparative considerations

LINKS	QUERY DATA
Help PolyPhen description *New!* PolyPhen mirror PolyPhen server at Harvard University *New!* SNP data collection Precomputed data for nsSNPs from dbSNP SNP data collection	Protein identifier (ACC or ID) from the SWALL database OR Amino acid sequence in FASTA format Position Substitution AA_1 * AA_2 *

PolyPhen

Predicts effect of an amino acid substitution on structure and function of a protein using physical and comparative considerations

http://coot.embl.de/PolyPhen/

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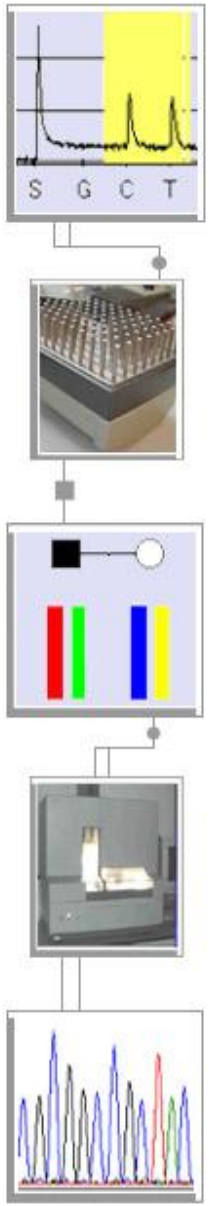
Challenges for the Future



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- ➢ **Ethical considerations**

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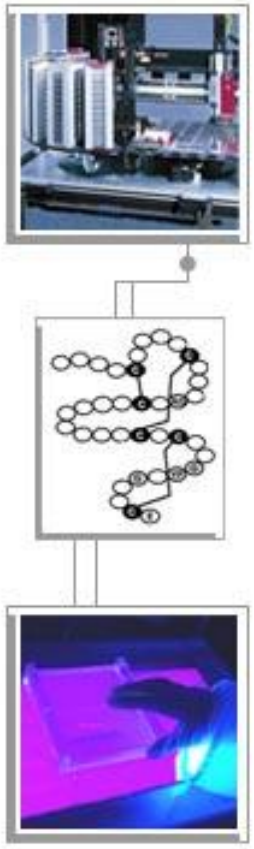
Ethical Considerations

- Patient Confidentiality and Consent
  - More tests on more people
  - How to use these genetic data
- Dissemenation of Knowledge
  - To less well Economically developed Countries
  - Because of Equal Opportunities
    - Instruments:
      - Exchange of Personnel
      - Collaboration
      - Courses
      - Workshops



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Thank you for your attention

Have a safe journey home