

European QC Materials

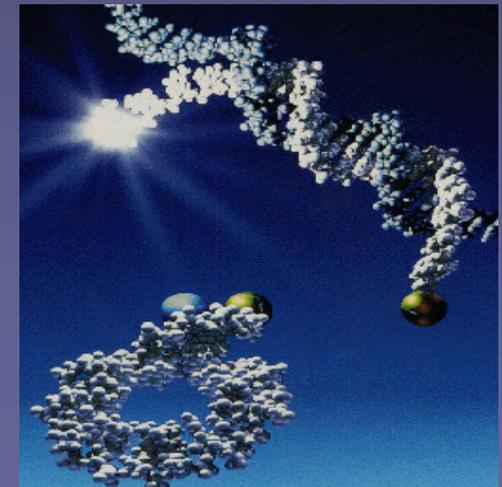
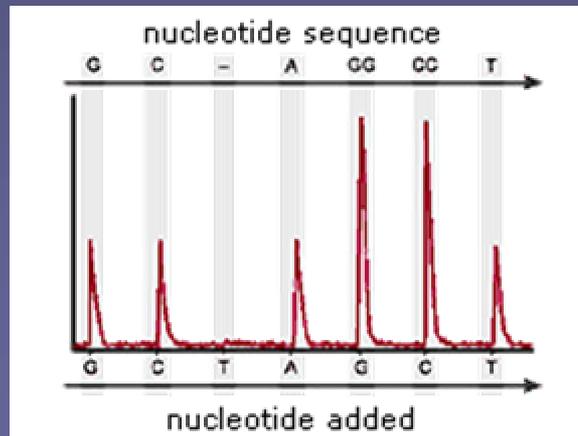
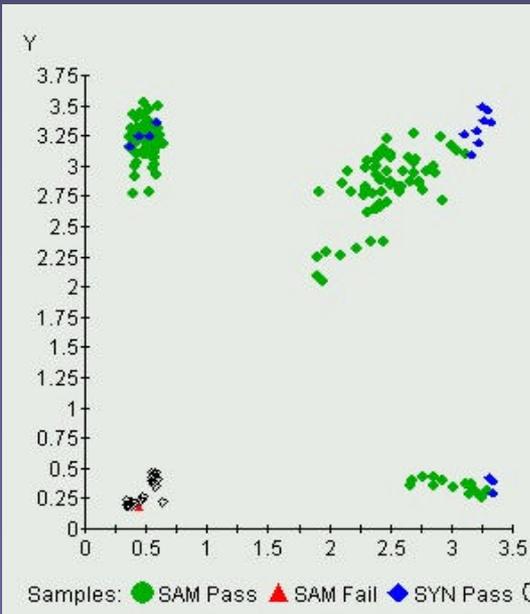
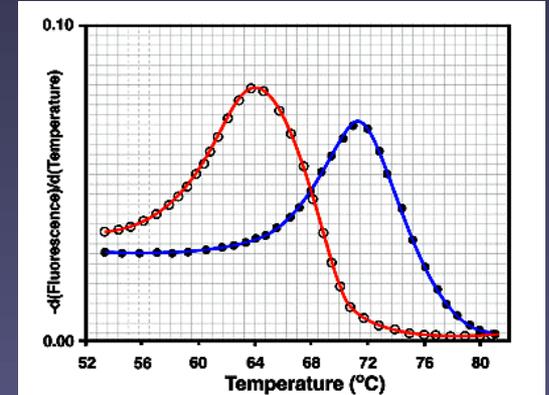
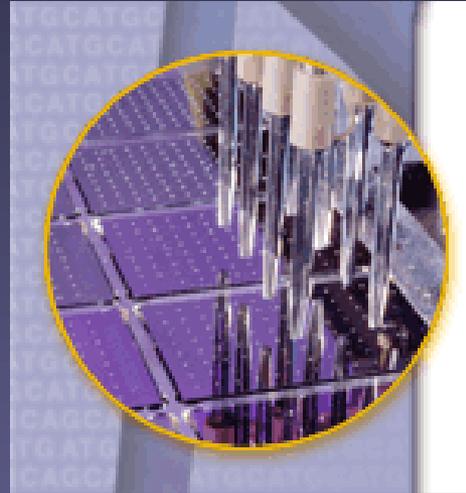
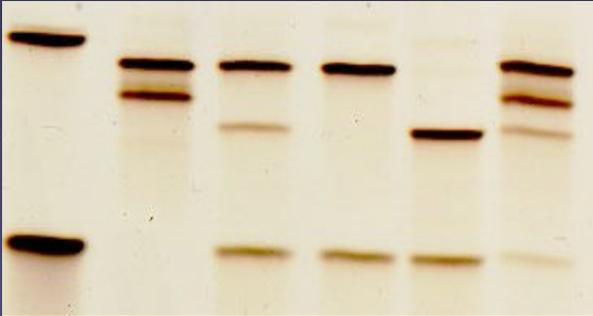
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Molecular genetic testing



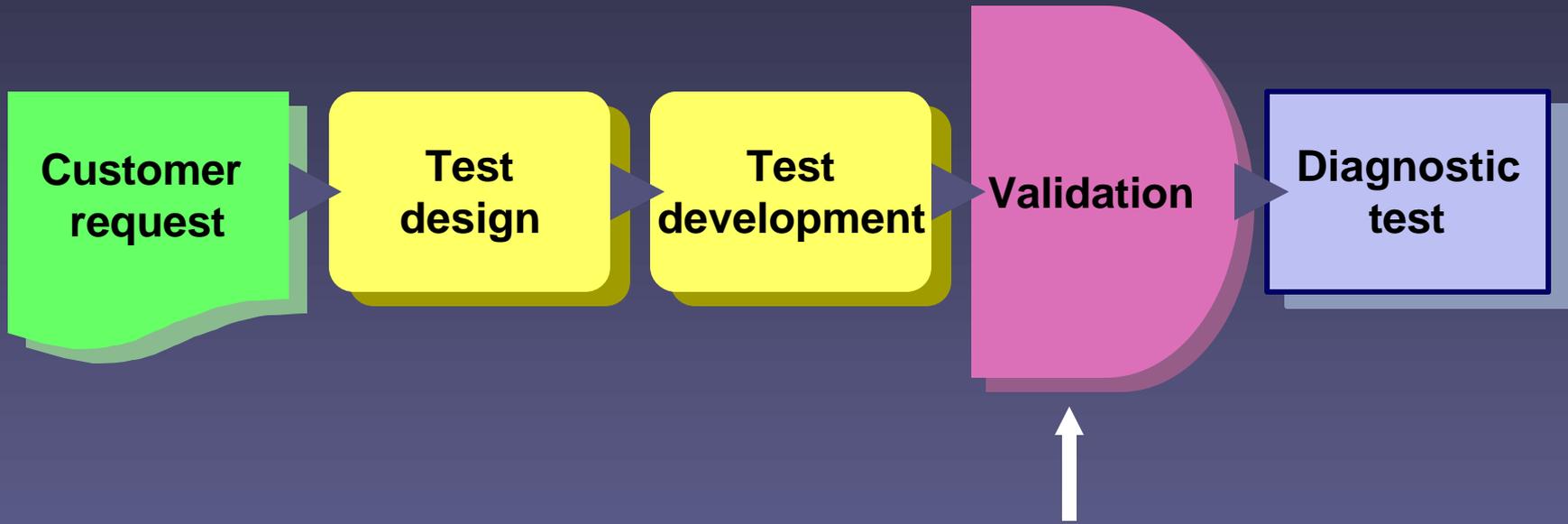
Quality

of the outcome of a genetic test

- Validate the applied method and technology
- Include a positive and negative control during the analysis
- Implement and maintain a quality assurance system in the lab
- Participate on a regular basis in quality assessment schemes

Key element: availability of quality control material

Validation of a test



Quality control material = reference material
Certified reference material ?

Reference Material ?

- Control material available from research laboratories
- Materials distributed by proficiency testing schemes

European EQA schemes for genetic diseases (national, multinational or international)

- Cystic Fibrosis
- Huntington disease
- Familial breast / ovarian cancer
- Duchenne and Becker Muscular Dystrophy
- Friedreich Ataxia
- Charcot-Marie-Tooth disease
- Fragile X-Syndrome
- Myotonic Dystrophy
- Hereditary non-polyposis Colorectal coli
- FAP
- Praderwilli and Angelman Syndromes
- Hereditary motor and sensory neuropathies
- Mitochondrial diseases
- Heridited hemochromatosis
- Spinal muscular atrophy
- Male infertility / deletions of the Y-chromosome
- Retinoblastoma
- Beta-thalassemia

Genotyping errors in the PT schemes

shortcomings in internal quality control material

e.g., EQA scheme for Cystic Fibrosis

Sample : I507del / wild type

Correctly typed by 113/136 laboratories (83%)

Incorrectly typed by 23 laboratories (17%)

typed as F508del / wild type or F508del / I507del

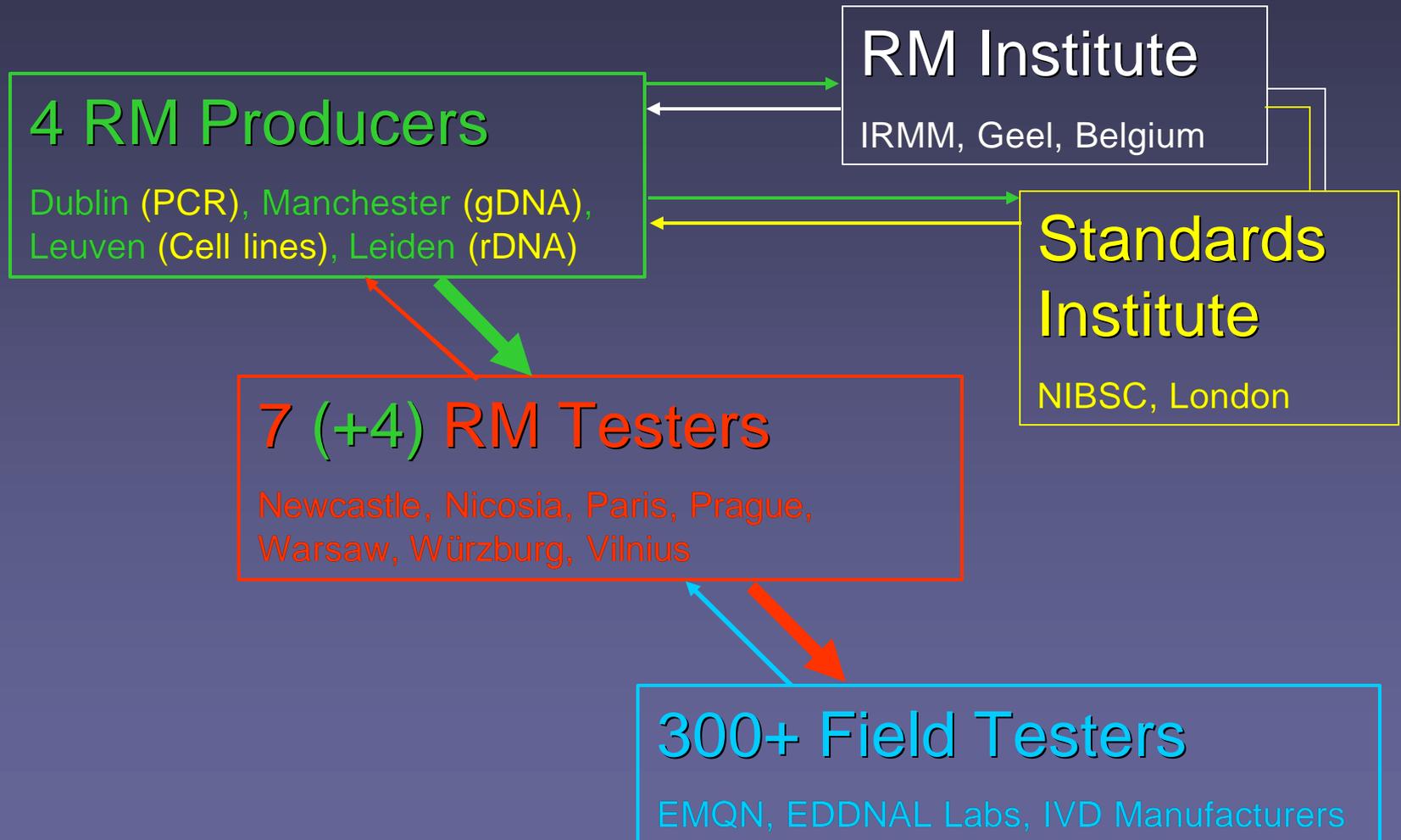
Reason:

no correct control material or do not have a control material

European Project
to Develop
Reference Materials
for Genetic Tests

The CRMGEN Project

CRMGEN Consortium Design



The CRMGEN project - RMs

Disorder	RMs to be developed	RM Type*
Cystic Fibrosis	Δ F508, G542X, G551D, N1303K	CL
Haemochromatosis	C282Y, H63D	PCR
Fragile X syndrome	Normal, premutation, expansion	CL, gDNA
Sickle cell anaemia	HbS	PCR
Beta thalassaemia	Codon 39 (C->T), IVSI- 110 (G->A)	PCR
Factor V Defect	R506Q (Factor V Leiden)	rDNA
Huntington Disease	Normal, CAG Expansions	PCR, rDNA
HNPC	Representative nonsense mutations	gDNA
SCA1-SCA7	Normal, CAG Expansions	PCR, rDNA
DMD	Deletions, duplications	rDNA

*KEY: CL, cell line; PCR, polymerase chain reaction product; gDNA, genomic DNA; rDNA, recombinant DNA

Green: Field testing

Blue: In development

White: Planned

Issues around RM format

Type	Similar to usual samples	Versatile	Stable	Economical to produce	Storage cost	Ethical issues
Cell Line	+++	+++	-	+	-	-
Genomic DNA	++	++	+	++	++	-
Recombinant DNA	+	++	++	+++	++	++
PCR Product	+	++	++	+++	++	++

+++

++

+

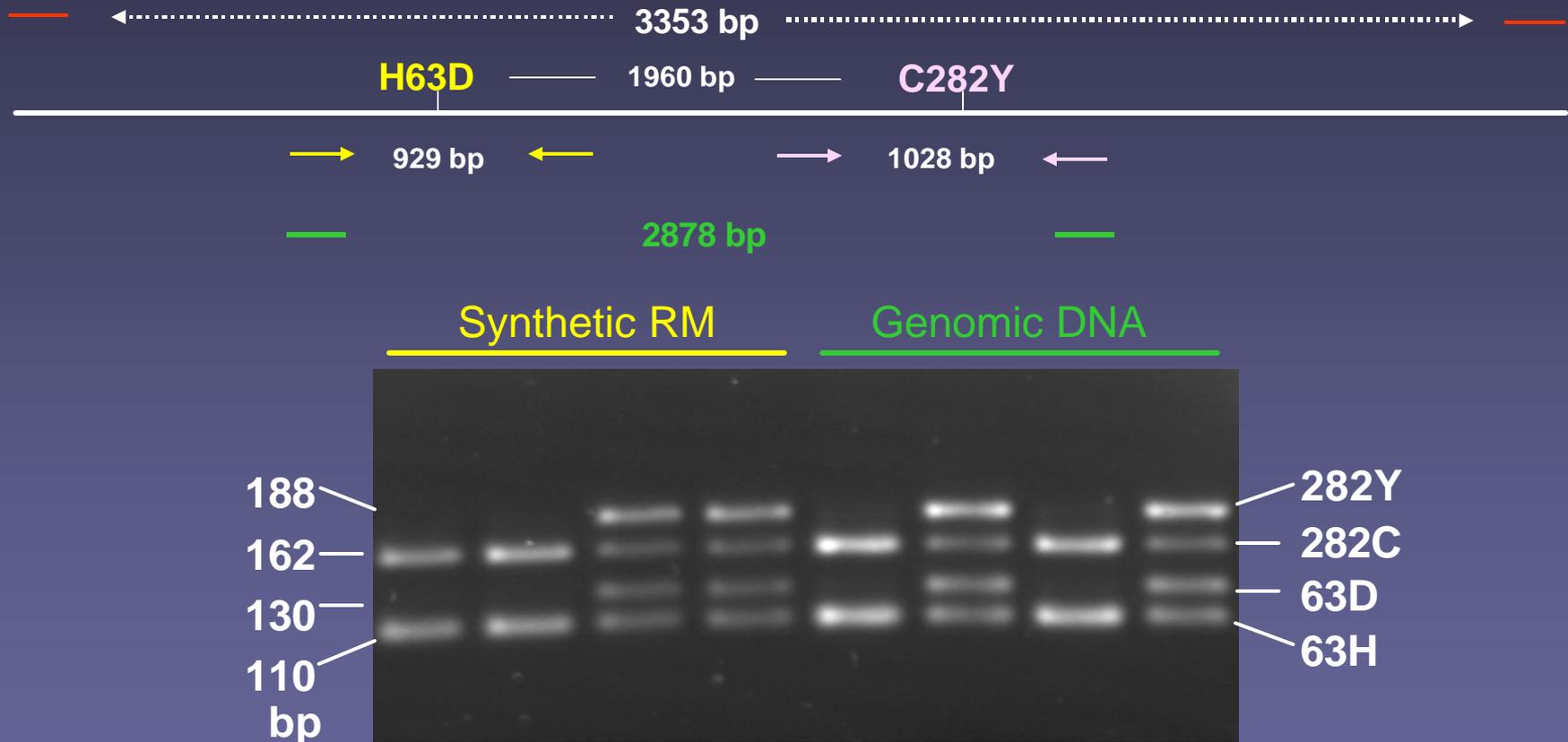
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More Favorable



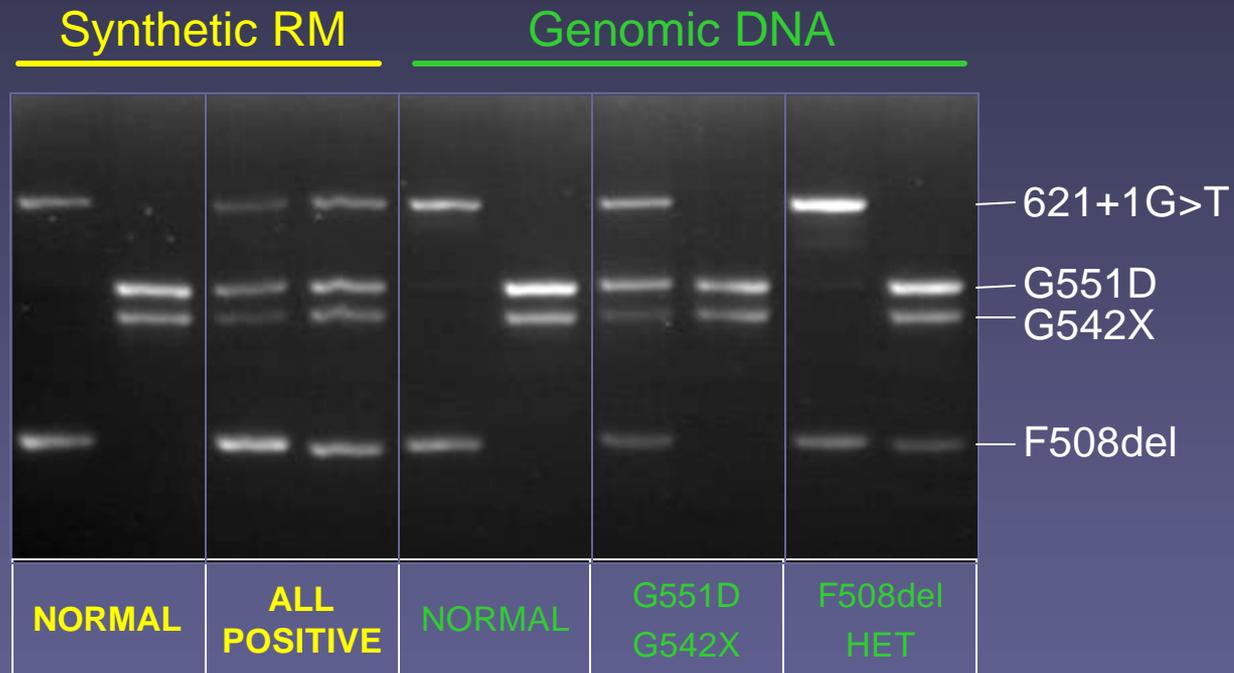
Less Favorable

CRMGEN: C282Y Duplex RM



BbrPI digest (Stott et al, 1999)

CRMGEN: CF Multiplex RM



ARMS™ PCR for four CF Mutations

Other European DNA RM Activities

● IRMM/IFCC

- Prothrombin G20210A mutation (wt, het, mut) final characterization in progress

● NIBSC

- Tissue Typing standards in routine production
- Factor V Leiden gDNA RM in progress
- Molecular Virology RMs

● LGC

- Generic PCR RM

The CRMGEN project - People

● Co-ordinator

- David Barton, Dublin

● Management Group

- Christoph Klein, Geel
- Jean-Jacques Cassiman, Leuven
- Bert Bakker, Leiden
- Glyn Stacey, London
- Rob Elles, Manchester
- Clemens Muller, Würzburg

● Partners

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- Roula Christodoulou, Nicosia
- Michel Goossens, Paris
- Milan Macek Jr, Prague
- Christine Mannhalter, Vienna
- Vaidutis Kuchinskas, Vilnius
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