

# Eurogentest Workshop on RMs for New Genetic Testing Technologies

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# paragonDx

- Spin-out from Gentris Corporation, started in August 2007.
- FDA registered manufacturer of Human Genomic Quality Controls (HGQC), Analyte Specific Reagents (ASR), and In Vitro Diagnostic kits.
- First 6 FDA cleared products are HGQCs for CYP2D6 genotyping
- First registered ASRs are components for CYP2C9 and VKORC1 variant analysis
- 510(k) submission for Rapid Genotyping kit for Warfarin therapy under review

# Recent events in US affecting genetic testing

- Two FDA cleared Warfarin sensitivity IVD products (CYP2C9 and VKORC1)
  - Nanosphere
  - Autogenomics
- Completion of CLSI MM-17, “Verification and Validation of Multiplex Nucleic Acid Assays”
  - Sec. 7= Reference and Testing Materials
    - Endogenous Nucleic Acid, WGA, Non-genomic RMs, Internal Controls

# Recent events in US affecting genetic testing

- Genetic Information Non-discrimination Act (GINA) makes it to the Senate floor for a vote after 13 years in the making (April 23, 2008)
  - Intended to prevent health insurers from discrimination of patients with genetic markers predicting future disease states
- Two companies launch Direct-to-Consumer genetic testing, providing whole genome scan of “patients” for disease susceptibility and personalized medicine
  - 23Nme
  - Navigenics

# Characteristics of HGQCs

- Developed, Designed, and Tested under GMP-QSR
- Manufactured, Labeled, Packaged under cGMP
- Rigorous QC process including bi-directional sequencing, integrity testing, and functional testing
- Class of regulatory compliance varies from RUO to IUO to IVD depending on intended use and claims

# Issues facing US manufacturers of Quality Controls

- FDA process is difficult, expensive, and at times not clear for a given application
- FDA can dictate regulatory compliance but currently has no oversight over CLIA-CAP laboratories in US
- CLIA (and CLSI) guidance on validation of QC material is outlined and fairly clear. Validation is not the same as GMP-QSR
- Currently no reimbursement for QC materials themselves, cost must be absorbed into the companion test

# FDA Guidance on Class II controls

- Issued January 10, 2007 by FDA-CDRH-OIVD

“A quality control material is a device intended to help monitor reliability of a test system by detecting analytical deviations such as those that may arise from reagent or instrument variation in genetic testing.”

## FDA Guidance (cont'd)

- “QC materials are used with a test system...”
  - Which system needs to be tested?
  - Only FDA cleared systems or more importantly laboratory developed tests (LDTs)??
- No real distinction made between “Process Controls” versus “Assay Controls” versus “Quality Controls” (lab, operator, lot of materials used, etc.)

# No Consensus Between FDA, CDC (CLIA), FTC, SACGHS and US Congress

- Three possible sources of human genomic DNA to be used as QCs
  - GMP-QSR
  - Left over patient samples
  - Research grade materials (e.g., Coriell)
- Claims of quality, “intended use”, and level of regulatory oversight is unenforced
- Leaves virtually NO commercial or financial incentive to make the highest quality product



# What about independent controls?

- Not possible to market “platform agnostic” controls
- FDA requires testing of any and all cleared platforms be used at external sites
- Impossible to know which platform will be utilized most for a specific control (RT-PCR, sequencing, invader, molecular beacons, hybridization arrays, etc.)
- Laboratory Developed Tests likely **NEED INDEPENDENT CONTROLS THE MOST!**

# Recommendations for Improved Quality Controls Used in the US Genetic Testing Industry

- Cover reimbursement of controls as some minimum needed to insure their usage in testing
- Create incentives for device manufacturers to produce GMP-QSR quality controls and RMs
- Put device manufacturers on the same playing field as other “not-for-profit” institutions
- Increase incentives and requirements for use of GMP-QSR material for laboratory developed tests (LDT)