The Development of Multigene Prognostic and Predictive Tests For Cancer Management

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Overview

- ❑ Critical factors in development of multigene assays
- ❑ DSA™ and Xcel Array technology
- ❑ Almac Col-Dx assay

Product Development Cycle

- ❑ In order for a biomarker to be successful it must address the following;
  - ➢ Clinical Utility
  - ➢ Clinical validation
  - ➢ Analytical validation

Design Control

DISCOVERY	DEVELOPMENT	VALIDATION	APPLICATION
Study design Discovery Technology Data generation Data analysis	Technology Migration Assay development All test components ready For independent validation (Hard/software/Reagents)	Analytical validation Clinical validation Regulatory submission Clearance/Approval	Test manufacture Test delivery (Kit, Service Lab)

Product Development Cycle

Almac - Biomarker Discovery Process

Planning Phase
Reagent & Materials
Initial study design
Data generation & assessment
Post processing: secondary study design & data matrix preparation
Exploratory analysis
Preliminary repeatability analysis
Model generation
Model evaluation & selection
Candidate model threshold selection
Candidate model repeatability analysis

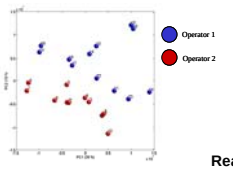
Study Design

Two critical components to study design:

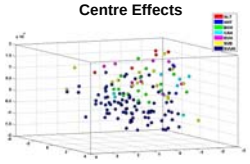
- ❑ **Biological:**
  - ➢ Representative population
  - ➢ Inclusion/exclusion criteria
  - ➢ Balancing for existing factors
- ❑ **Technical**
  - ➢ Tissue type
  - ➢ Instrumentation
  - ➢ Reagents (RUO Vs GMP)
  - ➢ Processing randomization

Importance of Randomization

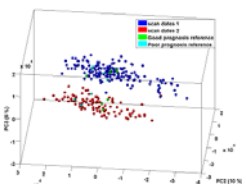
Operator effects



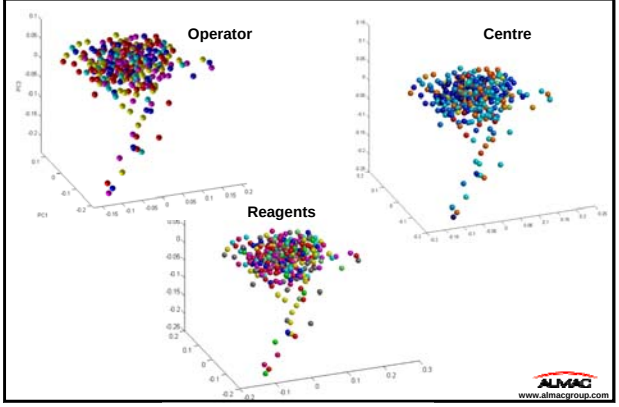
Centre Effects



Reagent Effects



Effect of Randomization: No Batch Effects



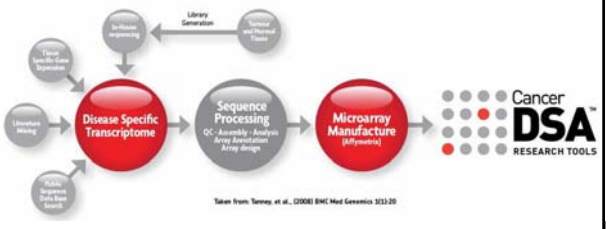
Overview

- Critical factors in development of multigene assays
- DSA™ and Xcel Array technology
- Almac Col-Dx Assay

Rationale

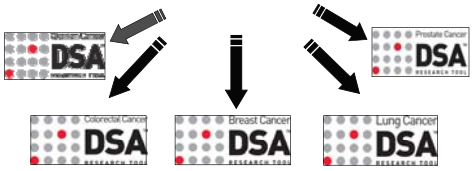
- **Required a stable solution the was optimally designed for biomarker discovery and validation**
- **Design considerations**
  - RNA based biomarker discovery (Microarray)
  - Maximum relevant content (Transcriptome based)
  - Disease Specific and cross disease application
  - Gold standard technology platform (Affymetrix)
  - GMP Manufacture
  - Optimised to work from FFPE

Generation of DSA™ Technology



Cancer DSA® Microarrays

Disease Transcriptome Focus

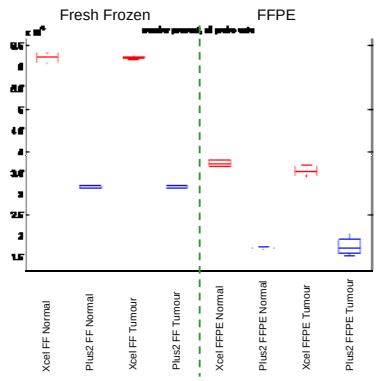


Multiple *Cancer DSA*™ research tools

Complete Relevant Transcriptome Information

Xcel ARRAY

Expression Detection



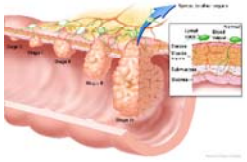
Number of Transcript detected is significantly higher on Xcel compared to Plus2 for matched samples

Overview

- Critical factors in development of multigene assays
- DSA™ and Xcel Array technology
- **Almac Col-Dx Assay**

Col-Dx Test

- **80% of patients with stage II Colon cancer are cured by surgery alone.**



- **20% will develop recurrence and should be offered chemotherapy following surgery.**
- **Aim is to develop a test to identify patients at high risk of relapse following surgery**

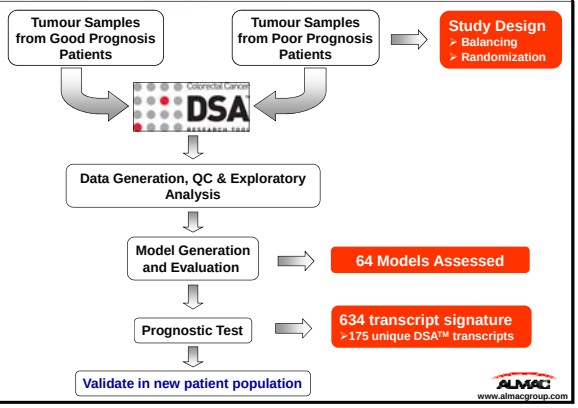
Balancing Factors For Test Generation

1) Sex
2) Hospital
3) Tumour content
4) Anatomical Site
5) FFPE block age
6) T-classification (T3/T4)
7) Patient age
8) Tumour differentiation
9) Lymphovascular involvement
10) Relapse time
11) Ethnicity
12) Patient performance score
13) Emergency presentation / residual tumor
14) Mucinous components
15) Number of lymph nodes retrieved
16) MSI

Contributing Clinical Centres

- St Vincents University Hospital, Dublin, Ireland – Dr. Diarmuid O'Donoghue
- Beaumont Hospital - Professor Elaine Kay
- Belfast, Northern Ireland – Dr Ultan McDermott
- University of Alabama, Birmingham, USA – Dr. Upender Manne
- Suburban Hospital, Bethesda, USA – Mr. William Smith
- University of Calgary, Alberta, Canada – Dr. Oliver Bathe
- Georgetown University, Washington, USA – Dr. John Marshall
- Karolinska Institute, Stockholm, Sweden – Dr. Ola Winqvist
- University Hospital Schleswig-Holstein, Kiel, Germany – Professor Holger Kalthoff
- Massachusetts General Hospital, Boston, USA – Dr. Sridhar Ramaswamy
- University of Pittsburgh Medical Centre, Pittsburgh, USA – Mr. Rajiv Dhir

Overview of the Study



Next Steps for Col-Dx

- **Studies for this year:**
  - Final clinical validation
- **Launch 2011**
  - CLIA assay initially
  - 510K approach agreed with FDA

Conclusions

- Study design and planning essential for biomarker discovery and validation
- DSA™ / Xcel technology represents a robust platform for biomarker discovery and validation from FFPE
- Using this approach we have developed the Col-Dx assay designed to improve the management of stage II colon cancer patients.

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- Richard Goldberg
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- Keith Kerr
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Collaborators

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•University of Pittsburgh Medical Center, USA.
•University of Alabama, USA.
•Suburban Hospital, Bethesda, USA.
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