

## 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

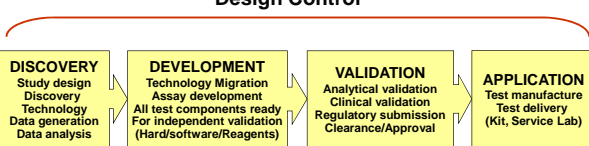


## Product Development Cycle


❑ In order for a biomarker to be successful it must address the following;

- Clinical Utility
- Clinical validation
- Analytical validation

**Design Control**




**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

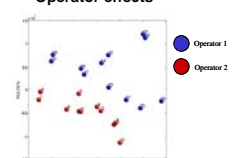
❑ **Technical**

- Tissue type
- Instrumentation
- Reagents (RUO Vs GMP)
- Processing randomization

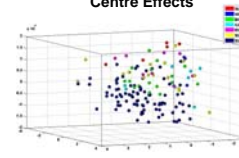


## Importance of Randomization

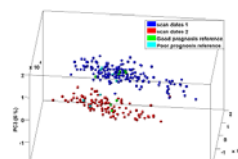
**Operator effects**




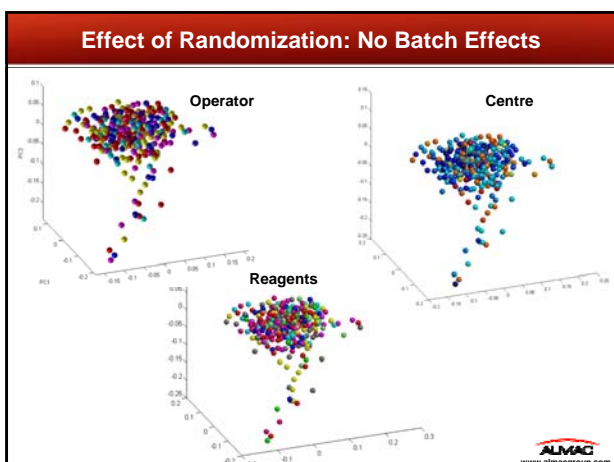
**Centre Effects**



**Reagent Effects**







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ALMAC  
www.almacgroup.com

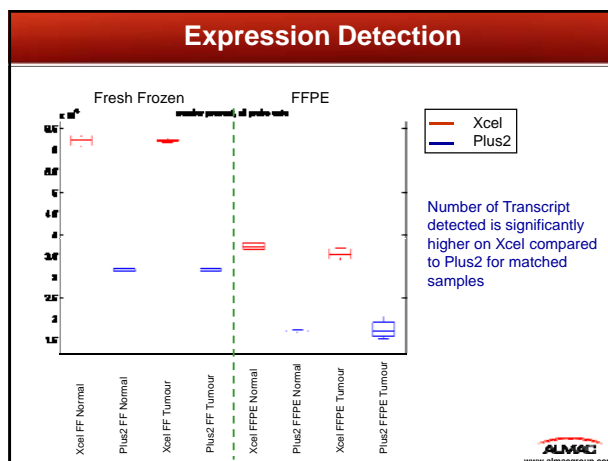
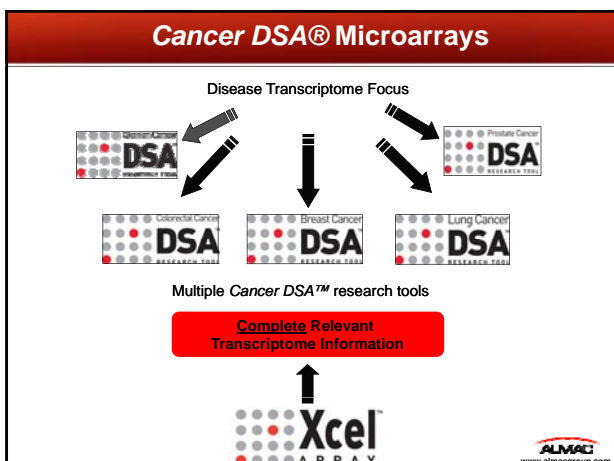
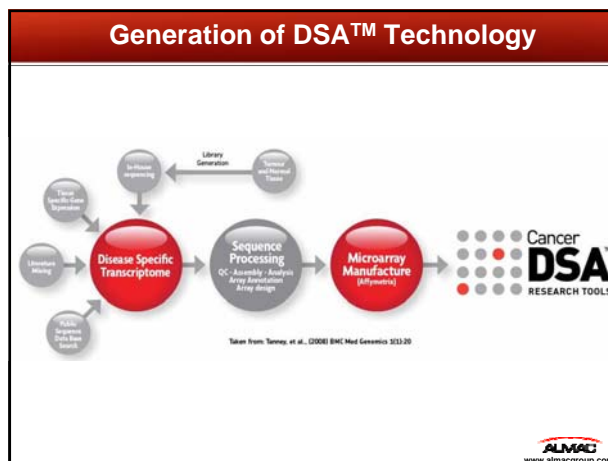
### Rationale

- 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

Xcel  
ARRAY


Cancer  
DSA  
RESEARCH TOOLS

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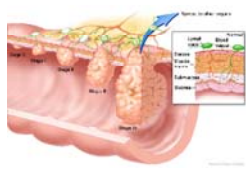
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### Col-Dx Test

- ❑ 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

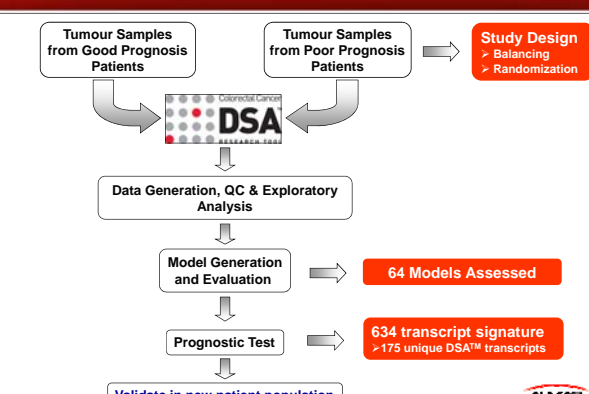




### Contributing Clinical Centres

- ❑ 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.**



## Acknowledgements

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- Steven Walker
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- Gavin Oliver
- Vitali Proutski
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- Andreas Winter and team

### Scientific Advisory Board

- Dan Sargent
- Al Benson
- Richard Goldberg
- Carmen Allegra
- Mike O'Connell
- Elaine Kay
- Keith Kerr
- Dean Fennell
- Patrick Johnston

### Collaborators

- MGH / Harvard University, USA.
- University of Pittsburgh Medical Center, USA.
- University of Alabama, USA.
- Suburban Hospital, Bethesda, USA.
- Georgetown University, USA.
- University of Calgary, Canada.
- Karolinska Institute, Sweden.
- University of Kiel, Germany.
- Royal Victoria Hospital / Queen's University, UK.
- St Vincent's Hospital, Dublin, Ireland.
- Beaumont Hospital, Dublin
- Queen's University of Belfast, UK.
- Dana-Farber Cancer Institute USA
- University of Colorado, USA
- University of Florida, USA
- University of Liverpool, UK
- University of Aberdeen
- Beatson Cancer Institute, UK
- Cambridge University, UK
- MD Anderson USA.
- University of Turin, Italy.

