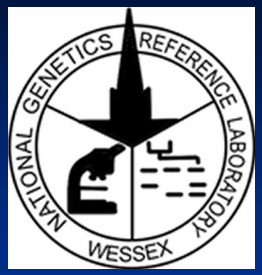


Implementation of The SCOBEC High Throughput Screening Facility

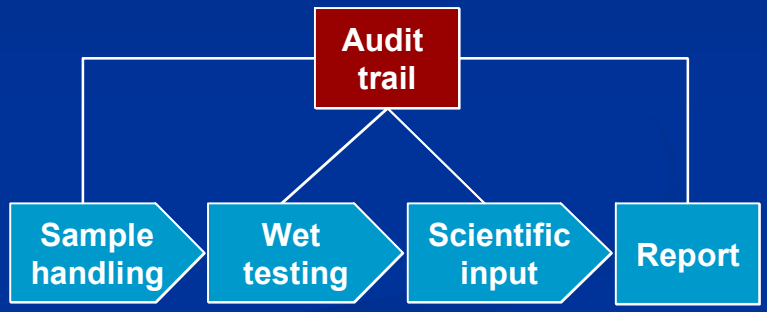
Project Leader: Chris Mattocks
Staff Involved: Dan Ward
Nick Owen
Dr. Helen White
Vicky Hall
Gemma Potts
Dr. John Harvey

Background

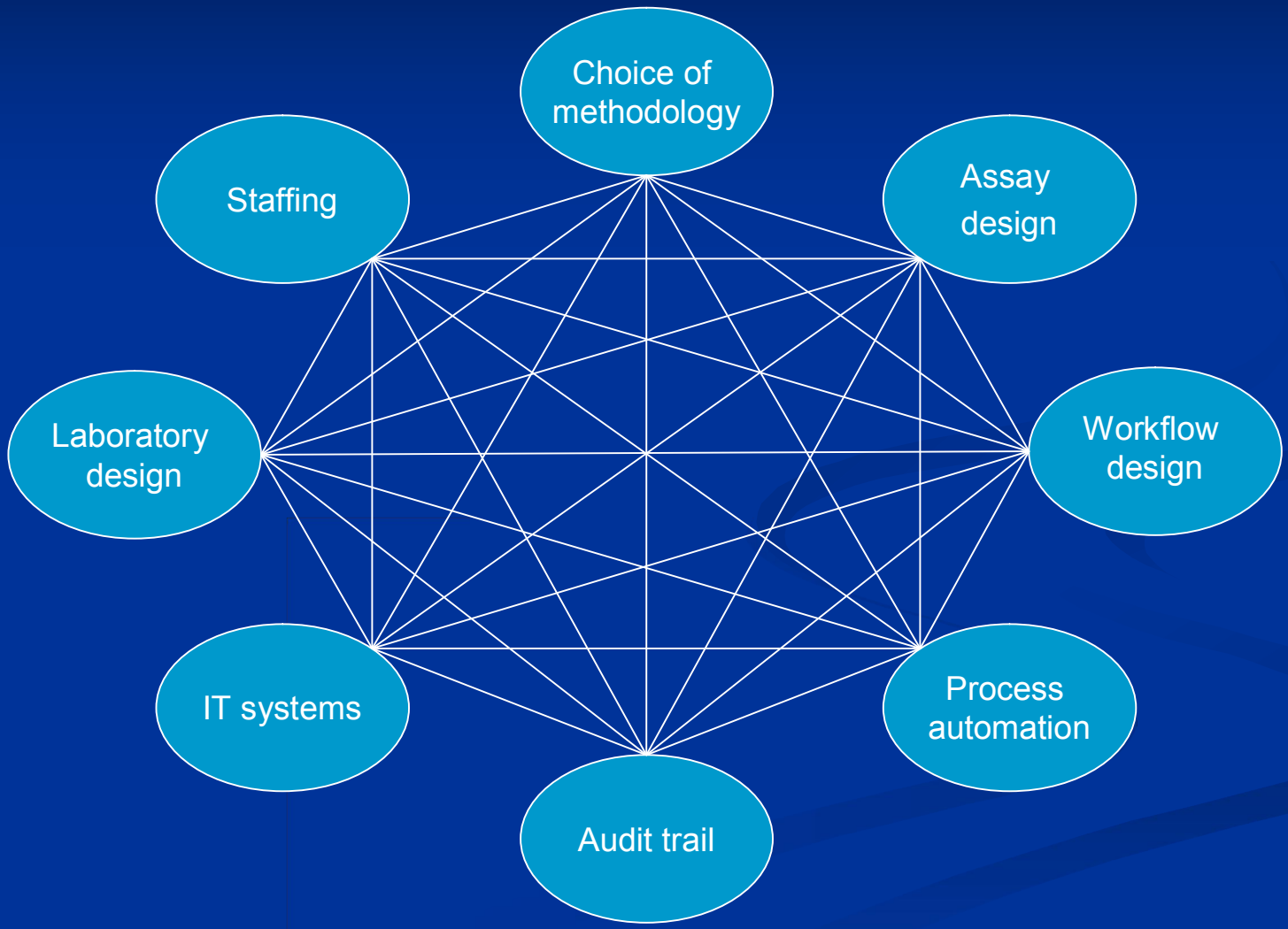
- Response to white paper guidelines for diagnostic testing of large genes
- Model, develop and implement future methods of working for genetic diagnostics

Aims

- Automate where possible
  - Increase TP / turnaround
  - Appropriate use of skill mix
- Flexible system
  - Different methodologies
  - Different diseases
  - Different capacity requirements
- Secure sample handling / audit trail

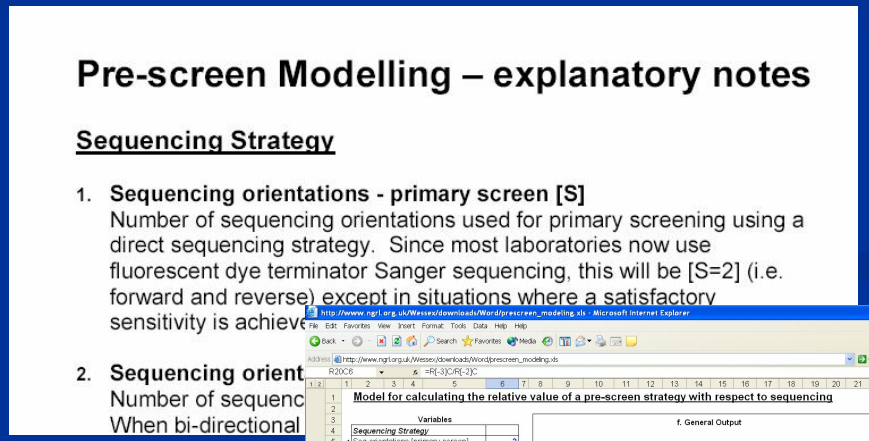


HTSF Implementation



Choice of Methodology

- General model to compare the relative merits of different screening strategies with respect to:
  - Cost
  - Throughput (samples/time)
  - Turnaround time (time/sample)
- Factors considered
  - Methodology
  - False positive rates
  - Failure rates
  - Size of test required (no of fragments)
  - Expected pick-up rate
  - Batching constraints

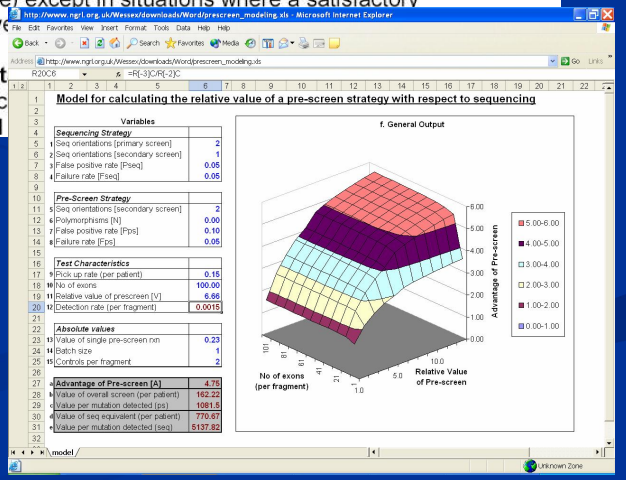


Pre-screen Modelling – explanatory notes

Sequencing Strategy

1. **Sequencing orientations - primary screen [S]**
   Number of sequencing orientations used for primary screening using a direct sequencing strategy. Since most laboratories now use fluorescent dye terminator Sanger sequencing, this will be [S=2] (i.e. forward and reverse) except in situations where a satisfactory sensitivity is achieve

2. **Sequencing orient**
   Number of sequenc
   When bi-directional



Model for calculating the relative value of a pre-screen strategy with respect to sequencing

f. General Output

No of exons (per fragment)

Relative Value of Pre-screen

Advantage of Pre-screen

Assay Design


National Genetics Reference Laboratory (Wessex)

NHS

Application Note

Standardised Primer Optimisation and Design Specification

NGRL WESSEX

May 2005

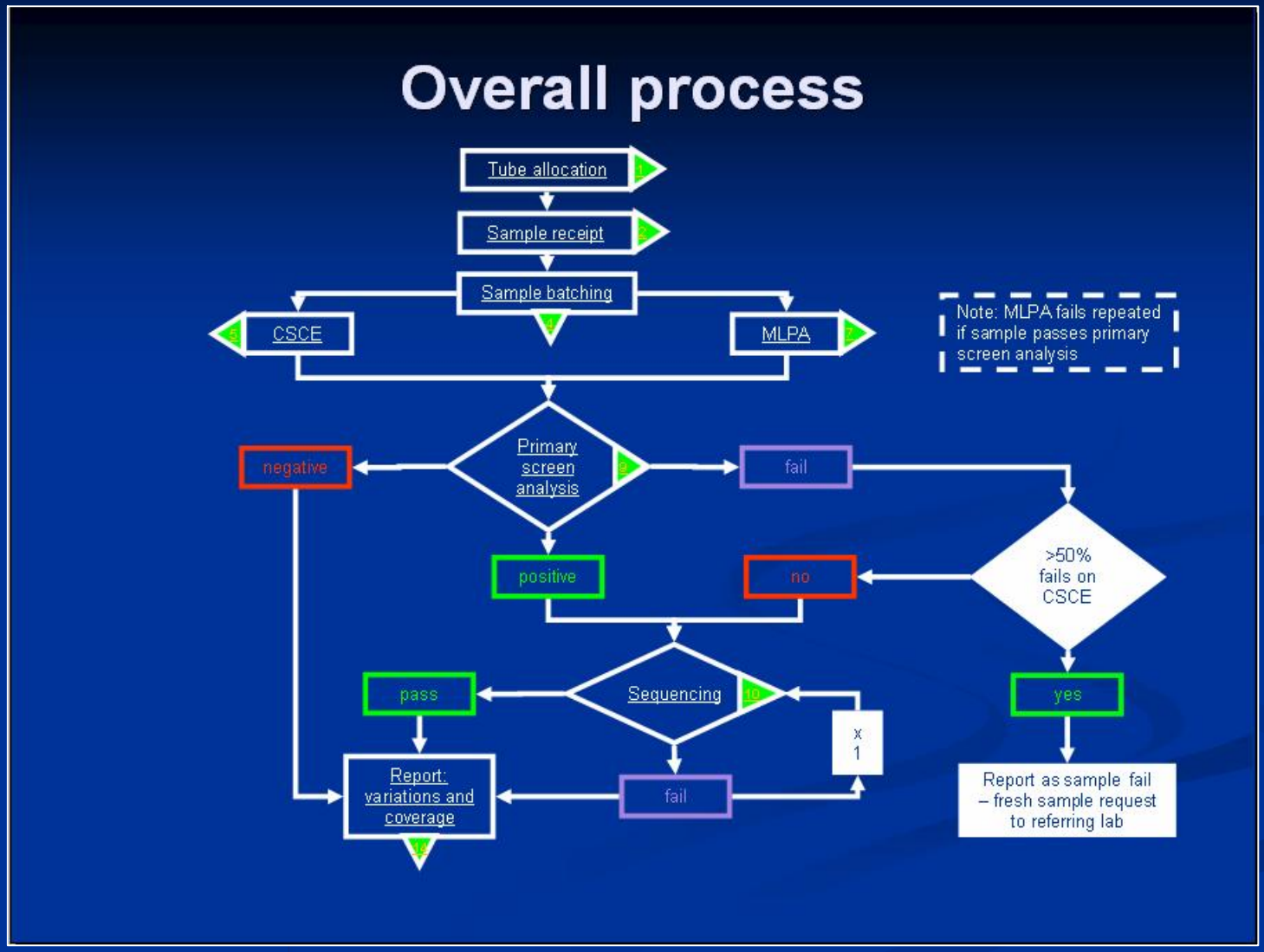
BRCA1 Primer set – BC1

Location	17q21-q24
Reference sequence (cDNA)	
Design basis (genomic DNA)	
Design date	
OMIM	
Excel spreadsheet	

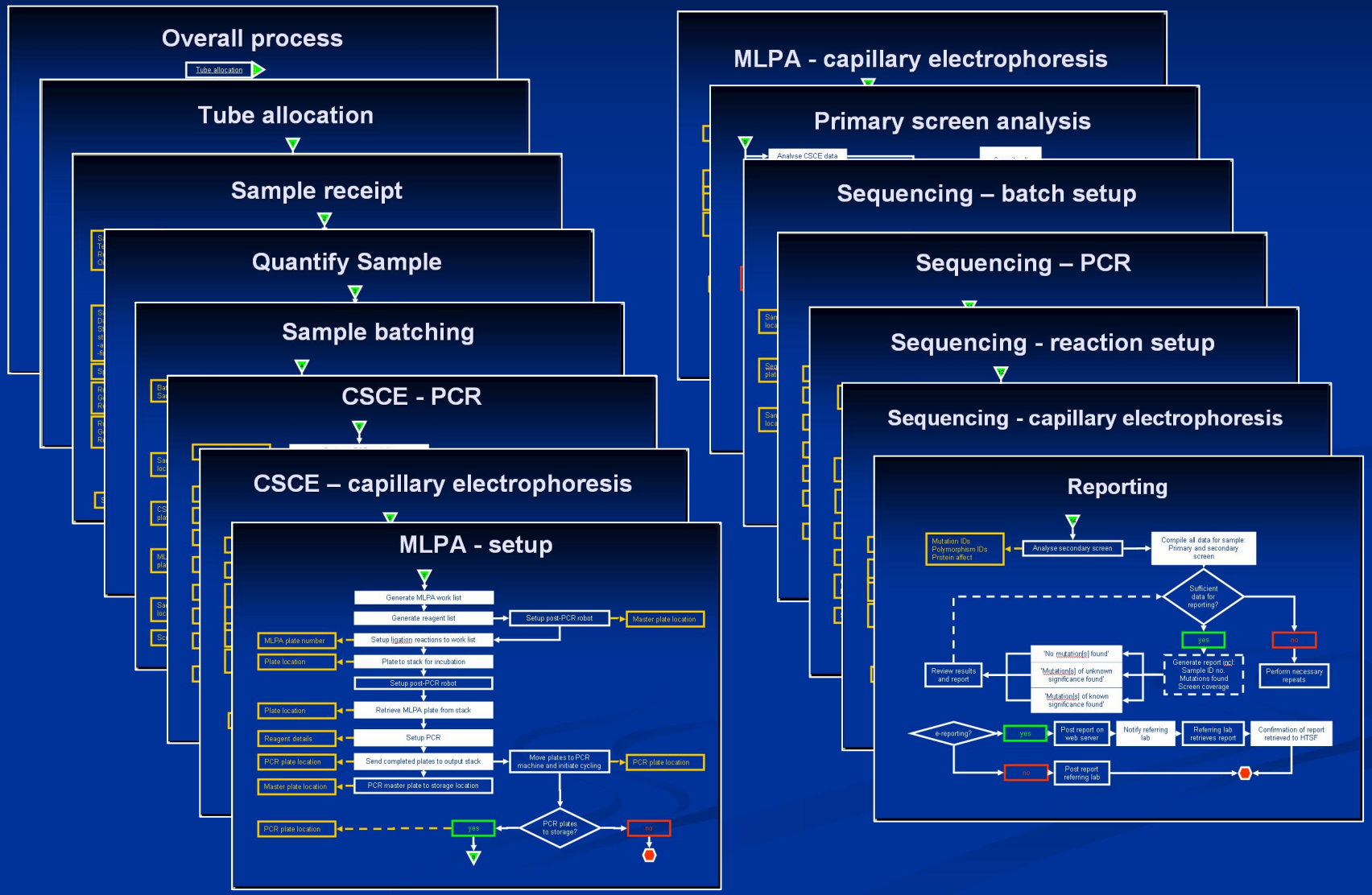
BRCA2 Primer set – BC2

Location	13q12-q13
Reference sequence (cDNA)	U43746 Nucleotide 1 = base 1
Design basis (genomic DNA)	Ensemble gene ID ENSG00000139618
Design date	31/3/05
OMIM	600185
Excel spreadsheet	BRCA2 primers 19_4_05.xls

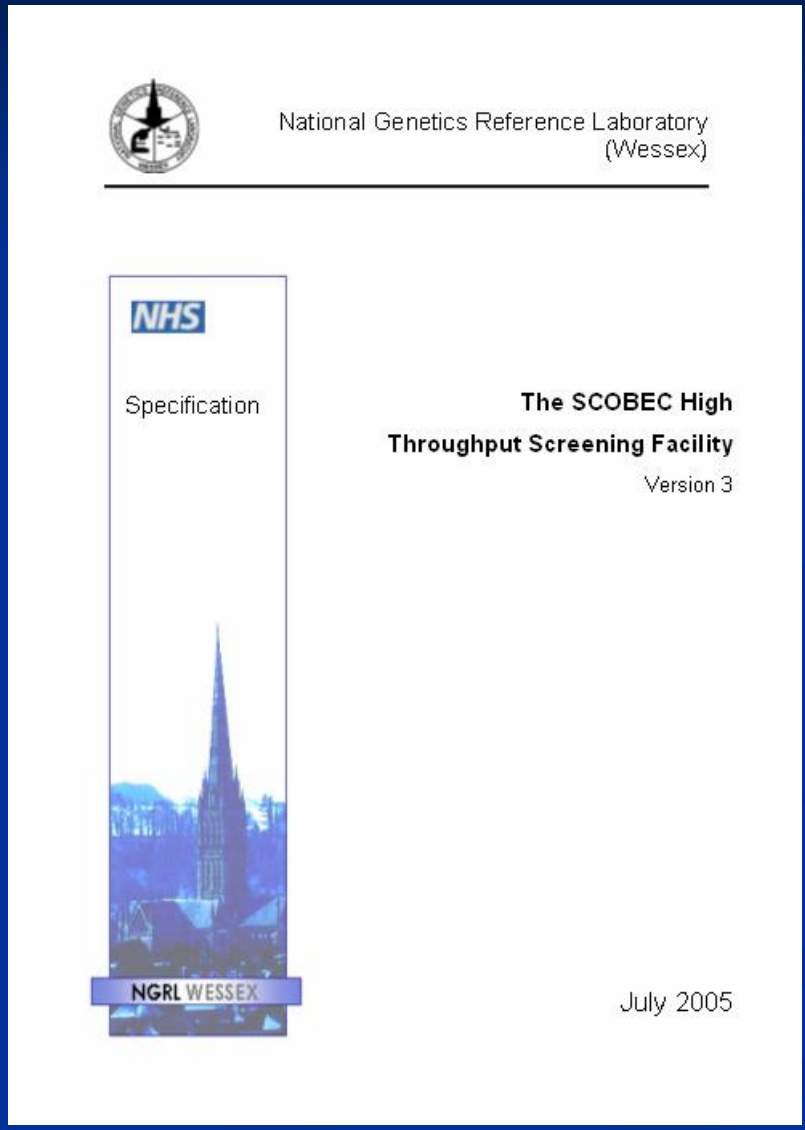
Workflow Design



Workflow Design



Workflow Design



National Genetics Reference Laboratory
(Wessex)

NHS

Specification

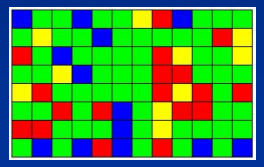
The SCOBEC High
Throughput Screening Facility

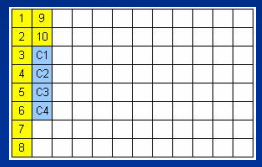
Version 3

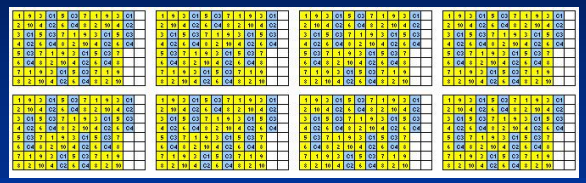
NGRL WESSEX

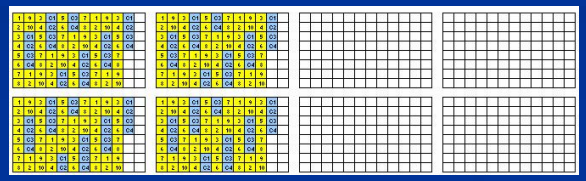
July 2005

Sample tracking



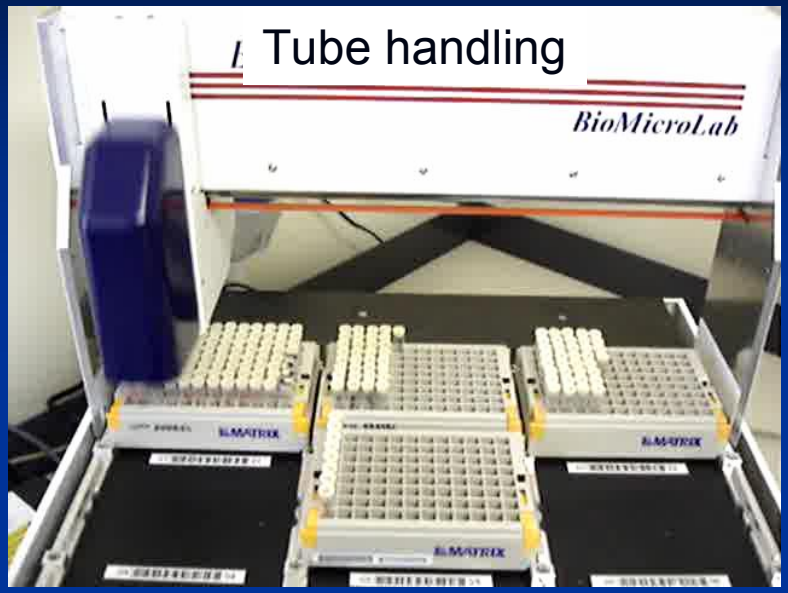


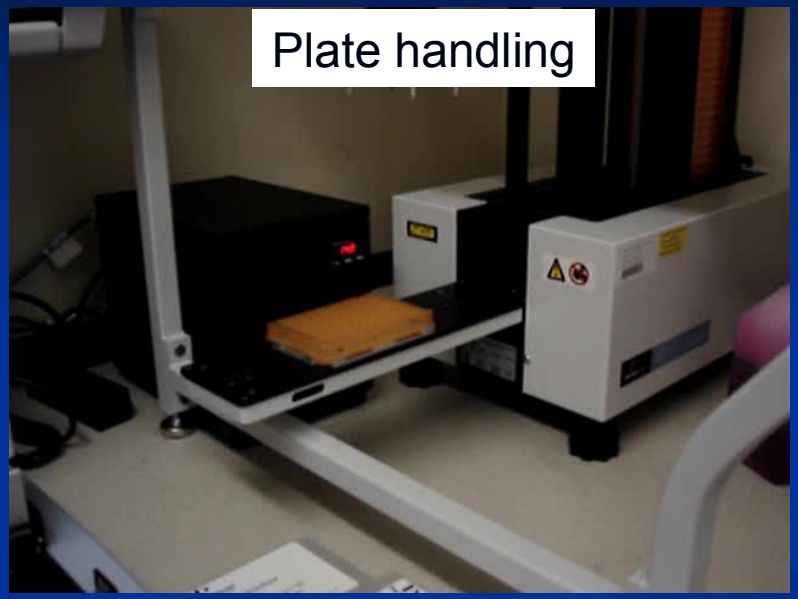


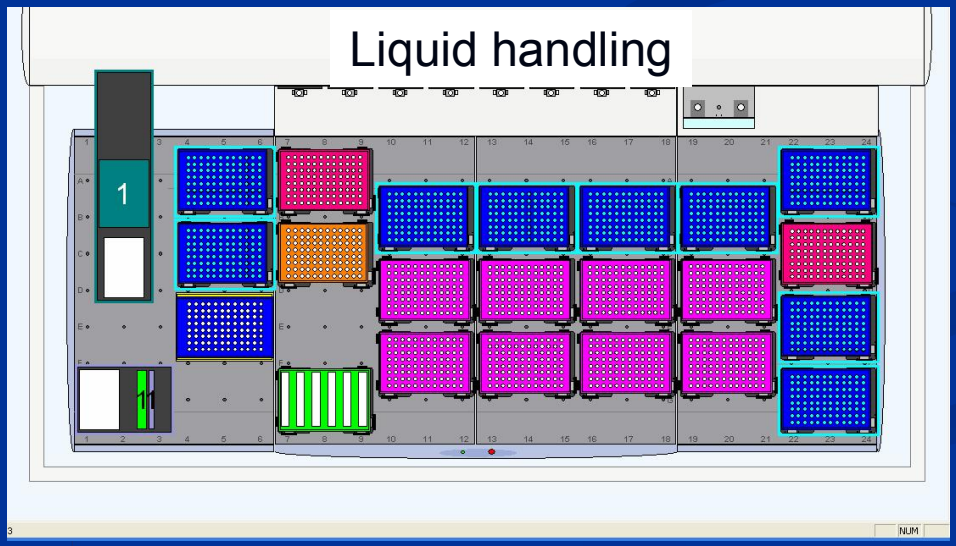


- Samples
  - Individual tubes in 96 racks
  - 2D barcode used as primary sample ID
  - Tube locations verified by plate bar-code scanner
- Batches
  - Sample tubes placed in empty rack by robot that checks bar-codes
  - Tubes replaced in correct storage location by robot
- Process plates (incl. reagents)
  - Plate IDs for all process plates are allocated automatically
  - Sample / fragment details assigned by well
- Instruments
  - Sample sheets created automatically
  - Sample sheets allocated in instrument by reference to plate bar-code

Process automation







Process Analysis

	BC1_08	BC1_19	BC2_07	BC2_08	BC2_09	BC2_12	BC2_13	BC2_14B	BC2_15	BC2_16	BC2_27A	BC2_27C	BC1_05	BC1_07	BC1_12	BC1_14	BC1_17	BC1_18	BC1_21	BC1_22	BC2_17	BC2_19	BC2_20	BC1_09	BC1_13	BC2_04	BC2_14A	BC2_18B	BC2_23	BC2_25	BC2_18A	% Fail
0035727865	F	N	F	F	F	F	F	F	S	F	F	F	F	N	N	F	P	F	F	F	N	S	F	S	P	N	F	S	N	N	N	67
0035727936	F	F	F	N	N	F	F	F	N	N	N	F	F	F	F	N	P	F	N	N	N	F	S	F	F	F	N	F	N	F	N	61
0035727852	F	F	F	N	F	F	F	F	N	F	F	F	F	F	F	N	N	F	F	N	P	F	F	N	N	N	N	N	N	N	N	61
0035727901	P	N	F	F	F	N	F	F	F	F	F	F	N	N	N	F	N	N	N	F	P	N	F	N	N	N	F	N	N	N	N	48
0035727925	F	F	N	S	N	F	N	N	N	N	N	N	N	F	F	N	N	N	N	N	P	N	N	F	F	F	N	F	N	F	N	39
0035727889	N	N	N	F	F	N	N	N	F	F	S	S	N	N	N	F	P	N	N	F	N	N	N	N	P	N	N	N	N	N	N	26
0035727934	P	F	N	S	S	S	N	S	S	S	N	N	N	N	N	N	N	N	N	N	N	S	S	S	S	N	N	S	N	S	N	15
0044202173	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	S	13
0035727862	P	N	N	S	S	N	S	S	S	S	S	N	N	N	S	N	P	N	S	N	P	S	S	S	P	N	N	S	N	S	N	9
0035727913	N	N	N	F	N	N	N	N	F	N	N	N	N	N	N	N	N	S	N	N	P	N	N	N	P	N	N	N	N	N	N	9
0035727854	P	N	N	N	N	N	N	N	N	N	F	S	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	S	N	7
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0035727853	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	S	N	N	P	N	N	N	N	N	N	7
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0035727430	N	N	N	N	N	N	N	S	S	N	N	N	N	N	N	N	N	N	N	S	P	N	N	N	S	N	N	S	N	N	N	4
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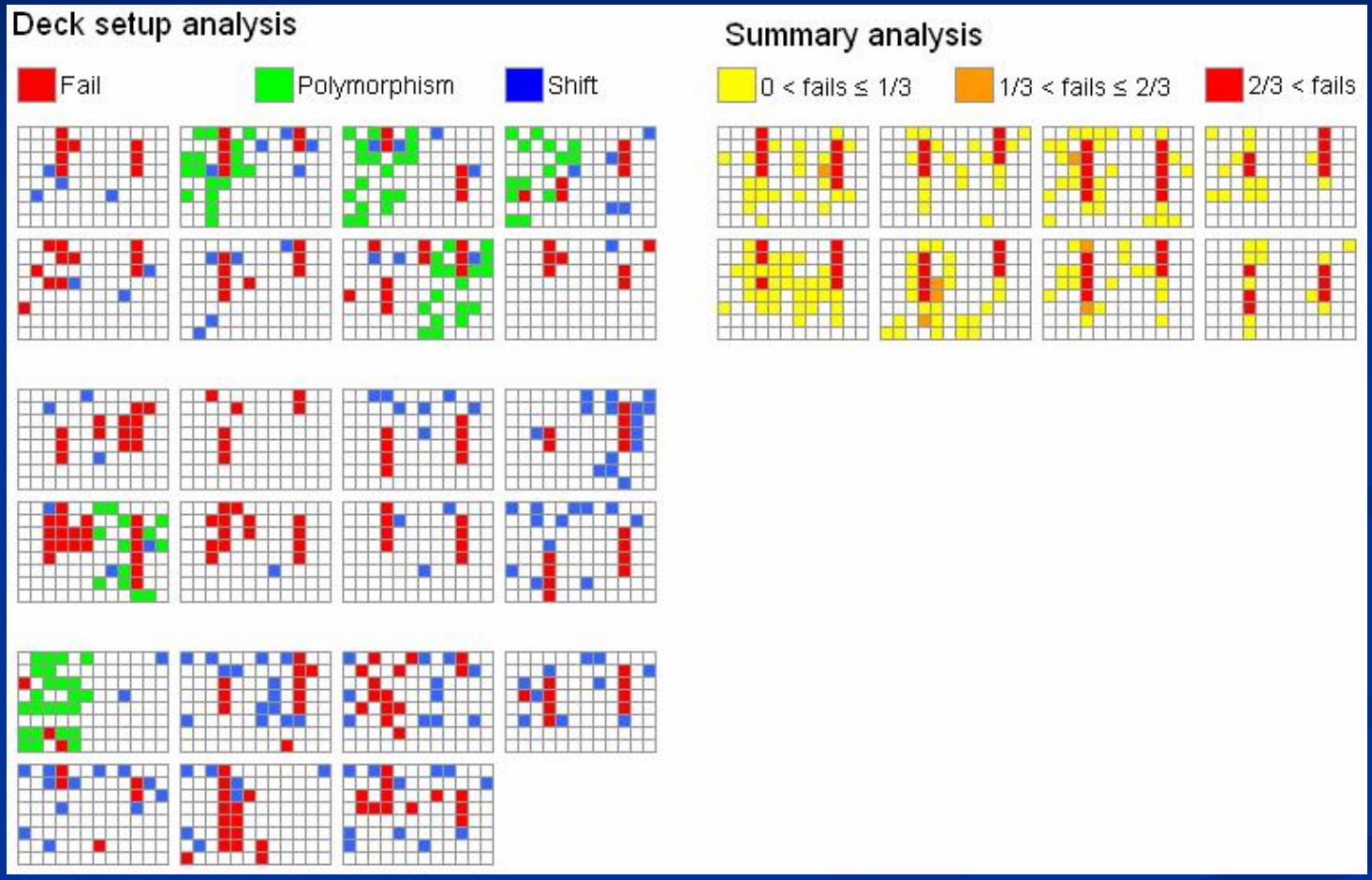
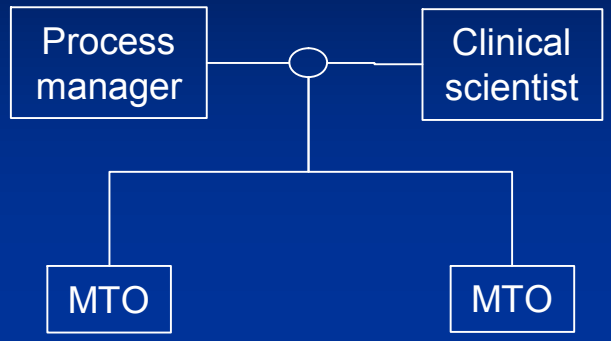
C1	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
C2	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
C3	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
C4	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
% Fail	8	8	8	8	8	8	8	8	8	8	8	8	6	6	6	6	6	6	6	6	6	6	6	4	4	4	4	4	4	0	10	

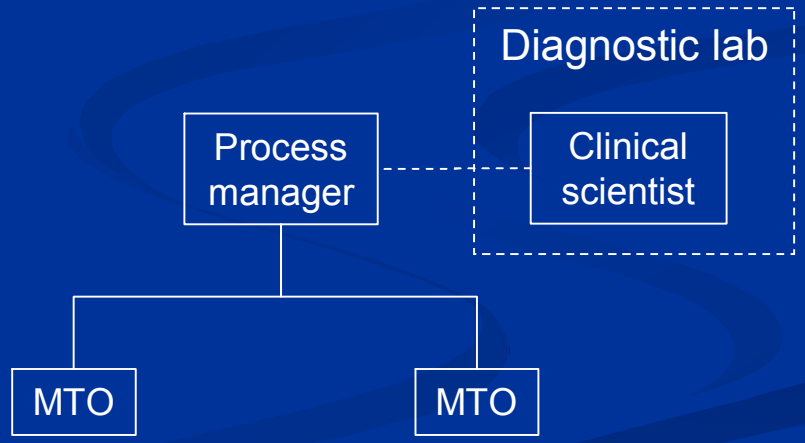
Process Analysis



Staffing

- Process manager
  - IT
  - Robotics
  - Workflow
- Clinical Scientist
  - Data checking (2° analysis)
  - Reports
- MTOs (x2)
  - Lab operation
  - 1° analysis



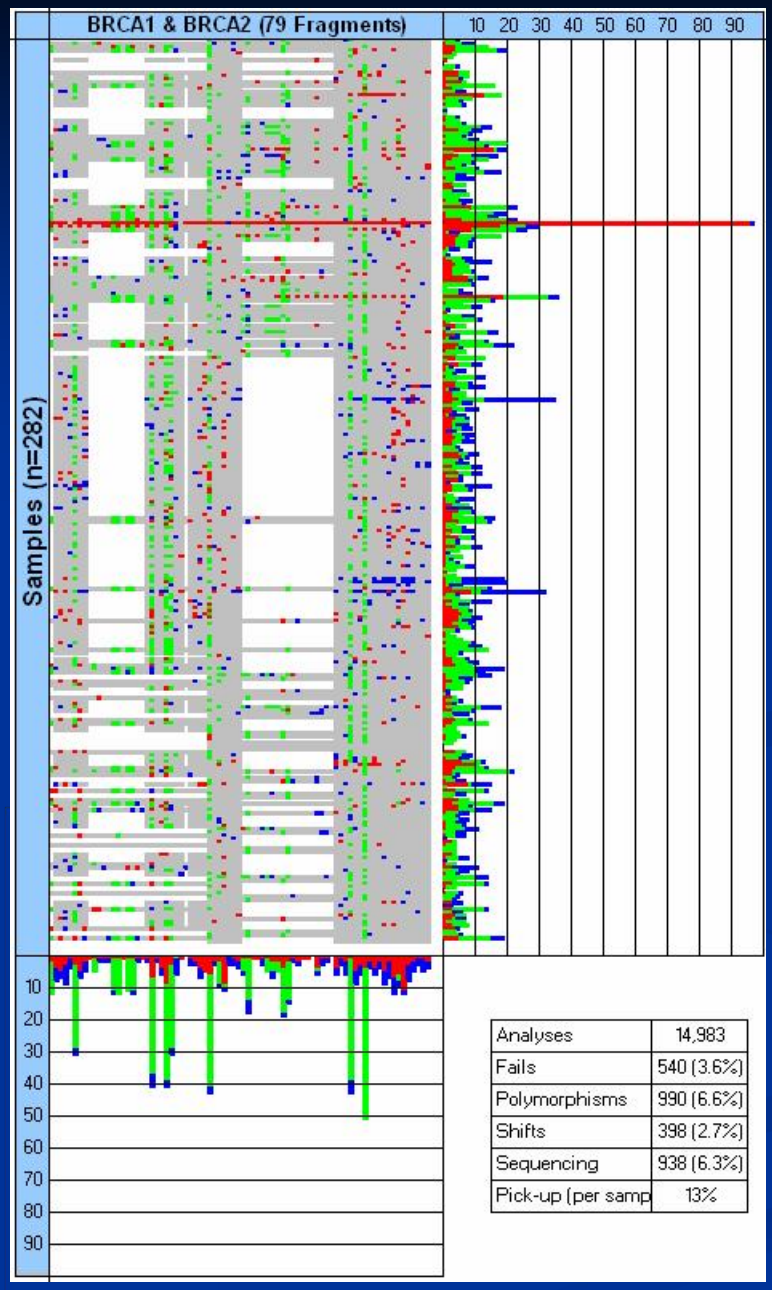


Implementation

1. Draft process set up and tested to resolve any problems
   - Automation
   - Audit trail
2. Final version build
   - Software written from principle (without the aid of draft)
   - All aspects checked against draft
3. Lab implementation

Status

	Process	Automation		Audit trail	
		Draft	Final	Draft	Final
	Sample registration	NA	NA	UC	UC
	Booking in	NA	NA	✓	✓
	Sample storage	NA	NA	✓	✓
Primary screen	Batch setup	✓	✓	✓	✓
Primary screen	PCR setup	✓	✓	✓	✓
Primary screen	Pooling	✓	✓	✓	✓
Primary screen	Instrument setup	✓	✓	✓	✓
Primary screen	Analysis	✓	UC	✓	UC
Secondary screen	PCR setup	✓	UC	✓	UC
Secondary screen	PCR clean-up	✗	✗	✓	✗
Secondary screen	Sequencing reaction	✓	✗	✓	✗
Secondary screen	Sequencing clean-up	✗	✗	✓	✗
Secondary screen	Instrument setup	✓	UC	✓	UC
Secondary screen	Analysis	✓	✗	✓	✗
	Reporting	✓	✗	✓	✗


BRCA1 & BRCA2 (79 Fragments)
10 20 30 40 50 60 70 80 90
Samples (n=282)
10
20
30
40
50
60
70
80
90
Analyses 14,983
Fails 540 (3.6%)
Polymorphisms 990 (6.6%)
Shifts 398 (2.7%)
Sequencing 938 (6.3%)
Pick-up (per samp 13%

Fully optimised system

	BC1_13	BC1_03	BC1_05	BC1_10	BC1_15	BC1_19	BC2_03	BC2_27C	BC1_06	BC1_07	BC1_08	BC1_09	BC1_12	BC1_14	BC1_16	BC1_17	BC1_18	BC1_21	BC1_22	BC1_23	BC1_24	BC2_02	BC2_04	BC2_05	BC2_07	BC2_08	BC2_09	BC2_12	BC2_13	BC2_14A	BC2_14B	BC2_15	BC2_16	BC2_17	BC2_19A	BC2_19B	BC2_19	BC2_20	BC2_21	BC2_22	BC2_23	BC2_24	BC2_25	BC2_26	BC2_27A	BC2_27B	% Fail
0035727869	N	F	F	F	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	7
0035727919	P	N	N	N	N	F	N	N	N	N	P	N	N	N	P	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	2
0035728296	N	N	N	N	N	N	N	F	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	2
0035728295	F	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	2
0035727901	F	N	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	2
0044202193	N	S	N	N	F	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	2
0044202240	P	N	N	N	N	N	F	N	N	N	P	N	N	N	P	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	2
0035727899	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0
0035728299	P	N	N	N	N	N	N	N	N	S	N	N	N	N	P	P	N	N	N	N	N	P	N	N	N	N	N	N	N	N	P	N	N	P	N	N	N	S	N	S	N	N	N	N	N	N	0
0035728297	P	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	N	N	N	N	N	P	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0
0035728294	P	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	0
0035727925	P	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	0
0035727936	P	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0
0035727852	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	0
0035727865	P	N	N	N	N	N	N	N	N	N	N	N	N	N	P	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0
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0044202205	N	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0
0044202230	N	N	N	N	N	N	N	N	S	N	P	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	0
0044202192	P	N	N	N	N	N	N	N	N	N	P	N	N	N	P	N	N	N	N	N	N	P	S	N	N	N	N	N	N	N	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0
0044202216	P	N	N	N	N	N	N	N	N	S	N	N	N	N	P	P	N	N	N	N	N	N	N	N	N	N	N	N	N	S	N	N	N	P	N	N	N	N	N	N	N	N	N	N	N	N	0
C1	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
C2	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
C3	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
C4	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	0
% Fail	8	4	4	4	4	4	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Maximising the impact of current investment in automation technology

Automation: current & potential

Type of testing	Automation	
	Current	Potential
Mutation scanning	Limited	✓✓
Genotyping (Targeted)	✗	✓✓
Methylation	✗	✓✓
Expression analysis (RNA)	✗	✓✓
Triplet repeats	✗	✗

Mutation scanning

Disease	Gene	OMIM	Scanning	Targeted	Confirmation	Tracking	Other	Total Tests 72526	Scanning tests 37225
ACANTHOSIS NIGRICANS ; AN	TWIST1	601622	Y	Y	Y		2	62	62
ACHONDROPLASIA ; ACH	FGFR3	134934		Y			1	59	0
ACYL-CoA DEHYDROGENASE, LONG-CHAIN, DEFICIENCY OF	HADHA	600890		Y	Y		1	138	0
ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN, DEFICIENCY OF	ACADM	607008	Y	Y	Y	Y	2	278	278
ADENOMATOUS POLYPOSIS OF THE COLON ; APC	APC	175100	Y	Y	Y		2	471	471
ADENOSINE MONOPHOSPHATE DEAMINASE 1 ; AMPD1	AMPD1	102770		Y	Y		1	5	0
ADRENAL HYPERPLASIA, CONGENITAL, DUE TO 21-HYDROXYLAS	CYP21A2	201910	Y	Y	Y	Y	2	168	168
ADRENAL HYPOPLASIA, CONGENITAL ; AHC	NR0B1	300473	Y		Y		1	20	20
ADRENOLEUKODYSTROPHY ; ALD	ABCD1	300371		Y		Y	1	162	0
ALAGILLE SYNDROME ; AGS	JAG1	601920			Y		0	20	0
ALBRIGHT HEREDITARY OSTEODYSTROPHY ; AHO	GNAS	139320	Y		Y		1	20	20

Total tests = 72,526
By scanning = 37,225
= 51%

'Large' genes ≈ 15%

Potential for Automation ≈ 36%

Total WLU (CMGS audit) ≈ 35.0M
x 36% = 12.6M

Divide by:
60 mins / hr
37.5 hrs / wk
48 wks / yr
29 labs

= 4 WTE per lab

Significant increase in capacity without further technology investment

The Batching Problem

- Liquid handling carried out on 96 of 384 well plates
  - Rarely enough of a single assay to fill a plate
  - Variable batch sizes due to unpredictable referral rates
  - For many tests a full batch is substantially <96

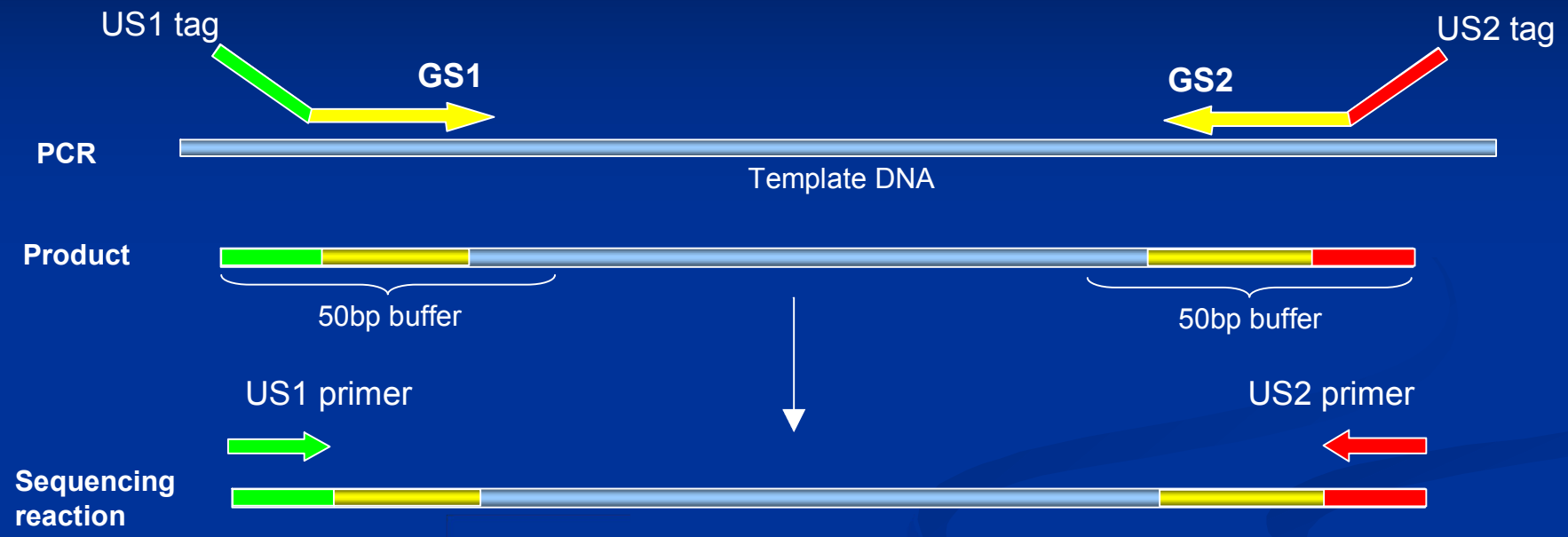
Standard batching

Variable batching

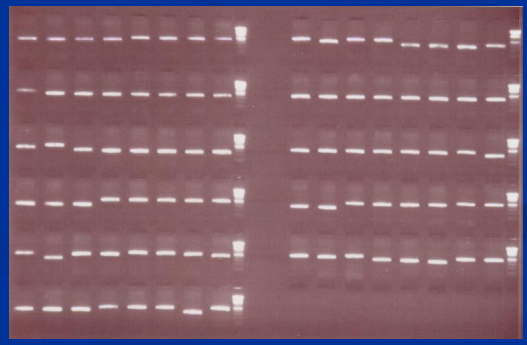
Flexible batching

- Standardised primer sets (annealing temp)
- Control of robotics

Standardised primer system:
Sequencing (unlabelled PCR)

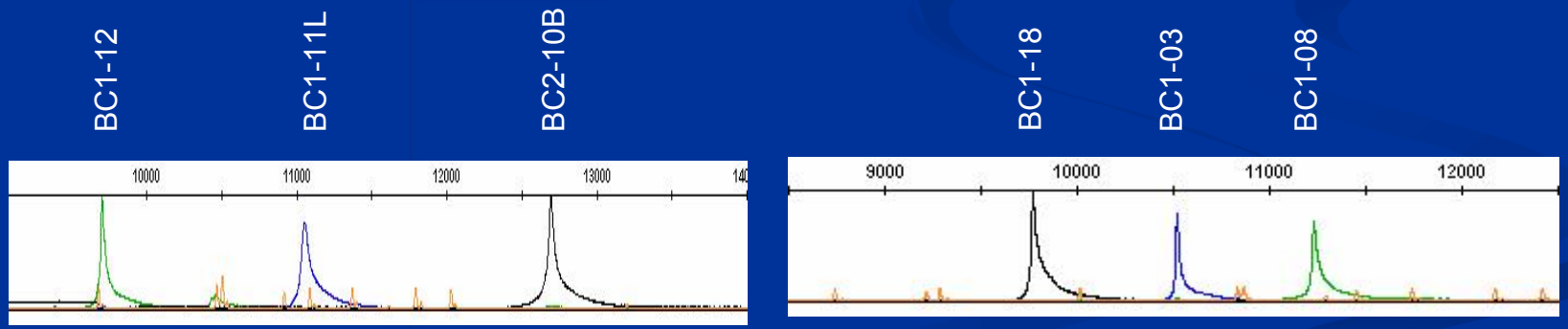


1	3	2	7	8	17	25	22	22	30	63
1	6	4	7	13	19	25	22	22	32	70
1	6	5	7	11	19	25	22	22	31	66
1	6	7	10	11	18	25	22	22	37	69
3	6	7	10	14	18	26	22	22	37	72
3	2	7	10	14	18	26	22	22	61	73
3	2	7	8	12	20	26	22	29	60	75
3	2	7	8	17	25	22	22	27	63	75



Standardised primer system:

Fluorescently labelled PCR



Automation: Control by Robot Protocol

- 1 programme for *each* plate layout
- Long and cumbersome to write
- Limited to standard batches only
- 1 test per batch

Aspirate from primer plate
    Well A01
Dispense to PCR plate
    Well A01
    Well B01
    Well C01
    Well D01
    Well E01
    Well F01
    Well G01
    Well H01
Aspirate from primer plate
    Well B01
Dispense to PCR plate
    Well A02
        etc…

Primer plate

PCR plate

Automation: Control by Worklist

- 1 programme for *any* plate layout
- Worklists generated by LIMS or simple spreadsheet
- Multiple tests per batch
- One off tests feasible
- Requires primer sets to be standardised across tests

(n)

Source plate	Dest. plate	Aspirate (a)	Disp 1 (b)	Disp 2 (b)	Disp 3 (b)	Disp 4 (b)	Disp 5 (b)	Disp 6 (b)	Disp 7 (b)	Disp 8 (b)
primer	PCR	1	1	2	3	4	0	0	0	0
primer	PCR	2	5	6	7	8	9	0	0	0

Repeat **n** times

Aspirate from primer plate
Well **a**
Dispense to PCR plate
Well **b**

Loop

	01	02	03	04	05	06	07	08	09	10	11	12
A	1	9										
B	2	10										
C	3	11										
D	4	12										
E	5											
F	6											
G	7											
H	8											

Primer plate

	01	02	03	04	05	06	07	08	09	10	11	12
A	1	2	4	7	9	14	18	20	20	23	29	
B	1	3	5	7	10	15	18	20	20	24	30	
C	1	3	63	7	11	15	18	20	20	25	31	
D	1	3	7	8	11	16	18	20	20	26	32	
E	2	3	7	8	12	16	19	20	20	26	33	
F	2	4	7	8	12	16	19	20	20	27	34	
G	2	4	7	9	13	17	19	20	21	28	35	
H	2	4	7	9	14	18	20	20	22	29	35	

PCR plate

Conclusions

- We have implemented a HT pipeline that:
  - Very high TP capacity
  - Gives a high degree of walk away automation
  - Gives flexibility to handle diagnostic referral patterns
  - Provides a high degree of security in sample handling and tracking
  - Allows detailed analysis of system errors or failures
- Key components:
  - Standardised primer system (annealing temp)
  - Simple generic Robot programmes
  - Automated control of robotics via work-lists

Acknowledgements

NGRL (Wessex)
Dan Ward
Nick Owen
Dr. Helen White
Vicky Hall
Gemma Potts
Dr. John Harvey

Sanger Institute - CSCE
Dr. Richard Wooster
Dr. Helen Davies

HTSF Staff
Julie Silibourne
Tracey Merifield
Stacey Sandell

IT infrastructure
Richard Renshaw
Richard Gibson

SDH Laboratory Setup
Dr. Tony Herbert
Jack Stone
David Dedman

CSOLS – system integration
Dr. Phil Goddard
Nikki Civil

Perkin Elmer – LIMS / Robotics
Malcolm Wall
Clive Stephens
Richard Willock

Applied Biosystems – CSCE
Chris Allen
Joop Theelen
Steven Berosik

Applied Maths – Analysis
Bruno Pot
Paul Vauterin