



On the Horizon: NGS as Companion Dx

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History of Companion Dx

- Prior to formal policy
 - ER/PR to direct therapy?
 - Not approved with a specific drug
 - Her-2/Herceptin
 - c-Kit, EGFR IHC, etc with respective drugs
- Dawning recognition that tests can be drivers of therapy

History of Companion Dx

- Policy needed
 - Patient safety
 - Predictability—plan for device element
 - Support for therapeutic approvals
- Policy creation
 - Change in drug development strategies to account for genetic information
 - PGx, VXDS discussions
 - Drug approvals without explicit direction to test

Changing Landscape of Companion Dx

- Multiple drugs with same/similar indication
- Multiple drugs within disease area
- Potential for “molecular diagnosis”
 - Drugs may cross disease lines easily



- Multiple tests for single disease
- Limited tissue
- Reimbursement

Challenges

- Minimize
 - Number of different tests needed
 - Tissue requirements
 - Incremental regulatory requirements
- Maximize
 - Information content per test

Next Generation Sequencing

- What it is:
 - Collection of technologies that enable rapid, affordable nucleic acid sequencing with improved sensitivity*
 - System: nucleic acid preparation, sequencer/reagents, several levels of software
 - Provide for sample to result capabilities

* theoretical; platform dependent

NGS as Companion Dx

- A model
 - Validated platform used to identify appropriate patients for clinical trial
 - Investigational mode
 - Data submitted to FDA in PMA to establish companion use
 - First PMA contains base set of information
 - Build panel over time, as new markers are identified
 - Single platform used to test for all relevant markers
 - Investigation-to-clinical use simplified
 - One platform needed in a lab to run all tests
 - Standardized, validated (national level?)



ABL1 BTK CTNNB1 FGF23 IL7R MLH1 PDGFRA SMO
AKT1 CARD11 DAXX FGF3 INHBA MLL PDGFRB
SOCS1
AKT2 CFBF DDR2 FGF4 IRF4 MLL2 PDK1 SOX10
AKT3 CBL DNMT3A FGF6 IRS2 MPL PIK3CA SOX2
ALK CCND1 DOT1L FGFR1 JAK1 MRE11A PIK3CG
SPEN
APC CCND2 EGFR FGFR2 JAK2 MSH2 PIK3R1 SPOP
AR CCND3 EMSY
(C11orf30) FGFR3 JAK3 MSH6 PIK3R2 SRC
ARAF CCNE1 EP300 FGFR4 JUN MTOR PPP2R1A
STAG2
ARFRP1 CD79A EPHA3 FLT1 KAT6A
(MYST3) MUTYH PRDM1 STAT4
ARID1A CD79B EPHA5 FLT3 KDM5A MYC PRKAR1A
STK11
ARID2 CDC73 EPHB1 FLT4 KDM5C MYCL1 PRKDC
SUFU
ASXL1 CDH1 ERBB2 FOXL2 KDM6A MYCN PTCH1
TET2
ATM CDK12 ERBB3 GATA1 KDR MYD88 PTEN
TGFB2
ATR CDK4 ERBB4 GATA2 KEAP1 NF1 PTPN11
TNFAIP3

ATRX CDK6 ERG GATA3 KIT NF2 RAD50 TNFRSF14
AURKA CDK8 ESR1 GID4
(C17orf39) KLHL6 NFE2L2 RAD51 TOP1
AURKB CDKN1B EZH2 GNA11 KRAS NFKBIA RAF1
TP53
AXL CDKN2A FAM123B
(WTX) GNA13 LRP1B NKX2-1 RARA TSC1
BAP1 CDKN2B FAM46C GNAQ MAP2K1 NOTCH1 RB1
TSC2
BARD1 CDKN2C FANCA GNAS MAP2K2 NOTCH2
RET TSHR
BCL2 CEBPA FANCC GPR124 MAP2K4 NPM1
RICTOR VHL
BCL2L2 CHEK1 FANCD2 GRIN2A MAP3K1 NRAS
RNF43 WISP3
BCL6 CHEK2 FANCE GSK3B MCL1 NTRK1 RPTOR
WT1
BCOR CIC FANCF HGF MDM2 NTRK2 RUNX1 XPO1
BCORL1 CREBBP FANCG HRAS MDM4 NTRK3
SETD2 ZNF217
BLM CRKL FANCL IDH1 MED12 NUP93 SF3B1
ZNF703
BRAF CRLF2 FBXW7 IDH2 MEF2B PAK3 SMAD2
BRCA1 CSF1R FGF10 IGF1R MEN1 PALB2 SMAD4
BRCA2 CTCF FGF14 IKBKE MET PAX5 SMARCA4
BRIP1 CTNNA1 FGF19 IKZF1 MITF PBRM1 SMARCB1

NGS Outstanding Issues

- Sponsor must choose to come to FDA
- Unknown how many platforms could meet FDA Quality System requirements
- Approved test systems tend to be static
 - Versus constant rev cycle of research use
 - Ability to rev at intervals will need to be worked out
- Validate NGS systems against already approved tests
- Can't substitute for IHC or other non-nucleic acid tests



- Thanks for your attention
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