


OMED COLORECTAL CANCER SCREENING COMMITTEE MEETING
Saturday, May 17, DDW San Diego, 2008
Presenter: D. Ahlquist



**World Organisation of
Digestive Endoscopy**

Colorectal Cancer Screening Committee Meeting


Stool DNA Testing

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DDW 2008, San Diego, USA
17, May, 2008

CRC Detection by Stool DNA Testing
Brief History

1992 Feasibility first established targeting a single marker (mutant K-ras)
 2000 Multi-marker assay with high detection rates for cancer and adenomas
 2004 **First multicenter study (EXACT funded)**
 2005 First commercial test, PreGenPlus (EXACT Sciences)
 2008 Stool DNA screening endorsed by American Cancer Society and Multi-Society Task Force
 2008 **Second multicenter study (NCI funded)**


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Stool DNA (PGP) vs Hemoccult (HO)
Multicenter Studies in Screening Setting

Test Positivity (%)

	EXACT (2507) ¹		NCI (2497) ²		
	PGP	HO	PGP	HO	HOS**
Cancer	52*	13	25	50	75*
Cancer/HGD	41*	14	36	41	55
Adv Ad	15	10	17*	6	16
Normal Colon	6	5	5	2*	4

¹Imperiale et al, NEJM 2004; 351:2704
²Ahlquist et al, DDW 2004,2007; *p < 0.05; **HOS = HemoccultSensa

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Stool DNA Screening
Obstacles to Effectiveness

- Biological
 - Molecular heterogeneity of tumors
 - Trace quantities of analyte
 - “Field changes” and false-positives
 - Microbial digestion of markers
- Technical
 - Incomplete DNA capture from stool
 - Analytical insensitivity
 - Limited throughput and costly assay platforms

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Stool DNA Screening
Future Approaches and Solutions

- More informative markers (DDW 2007)

At Least 1 Marker in Tissue

	<u>Adv Ad</u>	<u>Cancer</u>
PreGenPlus*	63%	60%
SDT-2**	98%	94%

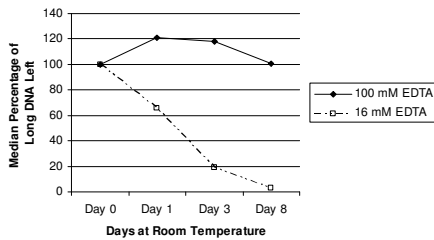
*23 point mutations
 **APC scan, Kras, Meth Vimentin

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Stool DNA Screening
Future Approaches and Solution

- Stabilization buffers added to stool



Zou et al CEBP 2006;15:1115

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Stool DNA Screening
 Future Approaches and Solution

- Higher analytical sensitivity (DDW 2008, Zou et al)

Stool Detection of Adv Adenomas (NCI Study)

	HO	HOS	PGP ¹	DMC ²
Sensitivity (27)	7	15	26	60*
Specificity (25)	92	92	100	92

¹PreGenPlus, ²Digital Melt Curve, *p<0.05 vs others

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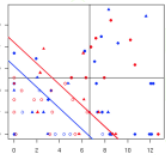
Stool DNA Screening
 Future Approaches and Solution


- Logistic models to refine accuracy with multiple markers* (DDW 2008, Xuan et al)

Comparative yields (CRN 54, Controls 26)

	Sens		<u>Spec</u>
	CRN	CRC	
Qualitative	78%	90%	88%
Quantitative*	76%	90%	96%

Markers (K-ras, BMP3 meth, hDNA)

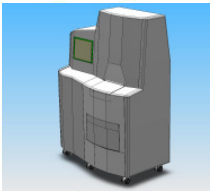


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Stool DNA Screening
 Future Approaches and Solution

- Deep sequencing with Next Gen sequencing technology

Simple prep
High throughput
Low test cost
 \$22 (1st generation)
 \$2 (2nd generation)



HeliScope™

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Summary

- Based on multicenter studies in screening setting, no clear advantages over FOBTs with 1st generation tests
- Biological and technical barriers
- Potential to improve accuracy, throughput, and affordability with next generation tools
- More research and development needed

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