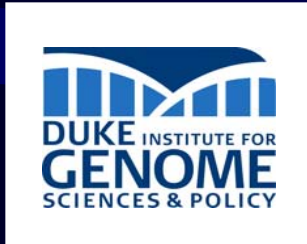


Type 2 Diabetes: A Model for Personalized Prevention

Alex Cho MD, MBA

Genomic Medicine Forum
November 1, 2007



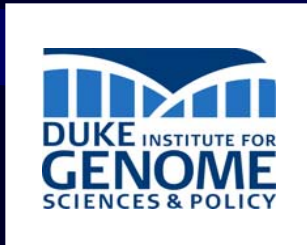
Agenda

- **Introduction**
- **Why Prevention?**
- **Why Type 2 Diabetes?**
- **Translational Challenges**
 - **Choosing Markers and the Message**
 - **Demonstrating Clinical Utility**
 - **Dealing with Externalities**
- **Duke Executive Health**
- **Future Directions**



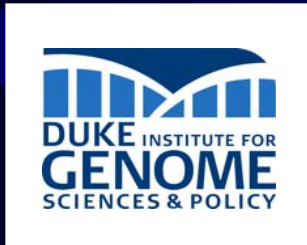
Introduction

- **Officially joined the Center in July**
- **Research interests included chronic illness, health behavior, technology**
- **Became interested in genomics at Fuqua**
 - talk on prospective healthcare by Ralph Snyderman
 - talk on pharmacogenomics by Allen Roses
- **Two missions**
 - establish a clinical service at Duke Exec Health
 - start a companion research program
- **Initially focused on diabetes**



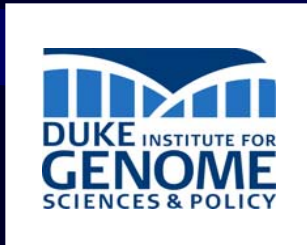
Why Prevention?

- **Genomics potentially powerful tool to rationalize imprecise practice**
- **Much of genomic information we have is limited to association with disease**
- **What prevention requires, genomics can deliver**
 - **Conditions w/ significant burden of suffering**
 - **Conditions w/ suitable natural history**
 - **Acceptable screening procedures**
 - **Treatments that work better early than late**
 - **Benefits outweigh harms**
 - **Benefits come at reasonable cost**



Why Prevention?

- **Examples**
 - **Type 2 diabetes**
 - **Breast cancer screening**
 - **Anticoagulation**
 - **Prostate cancer screening**
- **These conditions are also characterized by difficulty or controversy**

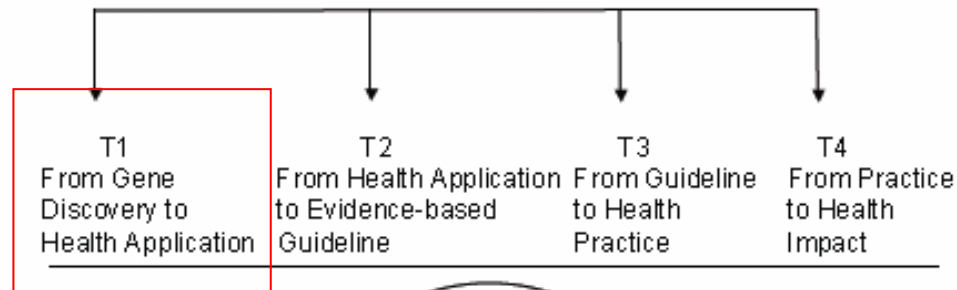


Why Type 2 Diabetes?

- **Huge burden**
- **Onset can be delayed, even prevented**
- **Current screening practice imprecise**
 - **FPG most common**
 - **USPSTF recommends screening only those w/ HTN, ↑chol; ADA recommends screening more broadly**
 - **NHANES III found that FPG alone would misclassify 20% of patients with diabetes as being nondiabetic**
 - **Oral glucose tolerance testing (OGTT) is more sensitive, but less convenient**
- **Clinical inertia around borderline results**
- **Well-studied markers, GWA studies**
- **Even an RCT showing benefit (DPP)**

Translational Challenges

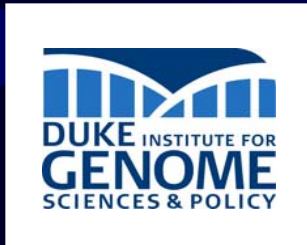
The Continuum of Translation and Translation Research for Genomic Applications in Population Health



**Evidence based
Guideline
Development**

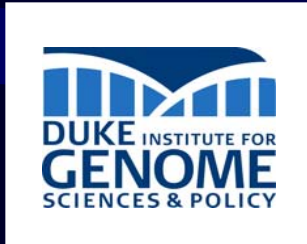
Infrastructure
Guiding Principles
Public-Private Partnership
Translation Research based on Knowledge Gaps

M Khoury 2007



Choosing Markers

- **A systematic review of literature to identify 'most-studied' SNPs associated with Type 2 diabetes risk**
- **With Eric Jiang, Timothy Robinson, Jeanette McCarthy, Lori Orlando**



Selection of SNPs

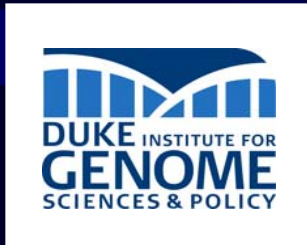
- **Two-step method:**

- **Step 1:**

- Identify all frequently studied SNPs and choose those with critical mass of literature. Cull top ~10 for Step 2.

- **Step 2:**

- Examine each of these top SNPs in detail to ensure adequate evidence base exists. Pull relevant articles for review and coding.



Selection of SNPs

- **Step 1 – select important SNPs**
 - **Perform search on disease of interest (1000+ articles)**
 - **Manually decide which studies are relevant to SNPs and disease risk (300+)**
 - **Tally the number of studies by gene symbol**
 - **Relatively easy-to-use unique identifiers, proxy for SNPs**
 - **Rank genes in order of number of studies**
 - **Select cutoff for detailed examination (Top 10)**
 - **Two-reviewer process was used, with disagreements adjudicated by a third reviewer**
 - **Approach allows for future pipeline of SNPs**



Step 1 search

"diabetes mellitus, type 2/genetics"[MAJR] AND ("genetic markers"[MeSH Terms] OR "polymorphism, genetic"[MeSH Terms] OR "genetic predisposition to disease"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms]) AND (hasabstract[text] AND "humans"[MeSH Terms] AND English[lang] NOT ("adolescent"[MeSH Terms] AND "child"[MeSH Terms] AND "infant"[MeSH Terms])) NOT review[PT] NOT ("haplotypes"[TIAB] OR ("messenger rna"[Text Word] OR "rna, messenger"[MeSH Terms] OR mRNA[Text Word]) OR ("mice"[TIAB] NOT Medline[SB]) OR "mice"[MeSH Terms] OR mouse[Text Word]) OR ("mitochondrial dna"[Text Word] OR "dna, mitochondrial"[MeSH Terms] OR mtDNA[Text Word])) OR diabetologia[All Fields] AND ("genetic polymorphism"[Text Word] OR "polymorphism, genetic"[MeSH Terms] OR (SNP[All Fields] OR polymorphism[Text Word]))

Which markers?

Established

- **PPAR gamma**
- **TCF7L2**
- **CAPN10**
- **KCNJ11**

Previously studied

- **ABCC8 (SUR1)**
- **ACE**
- **HNF1 alpha (MODY3)**
- **HNF4 alpha (MODY1)**
- **IL-6**
- **PGC-1**

Emerging

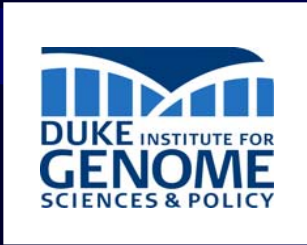
- **HHEX/IDE**
- **SLC30A8**
- **CDKN2A/2B**
- **IGF2BP2**
- **CDKAL1**

Step 2 search

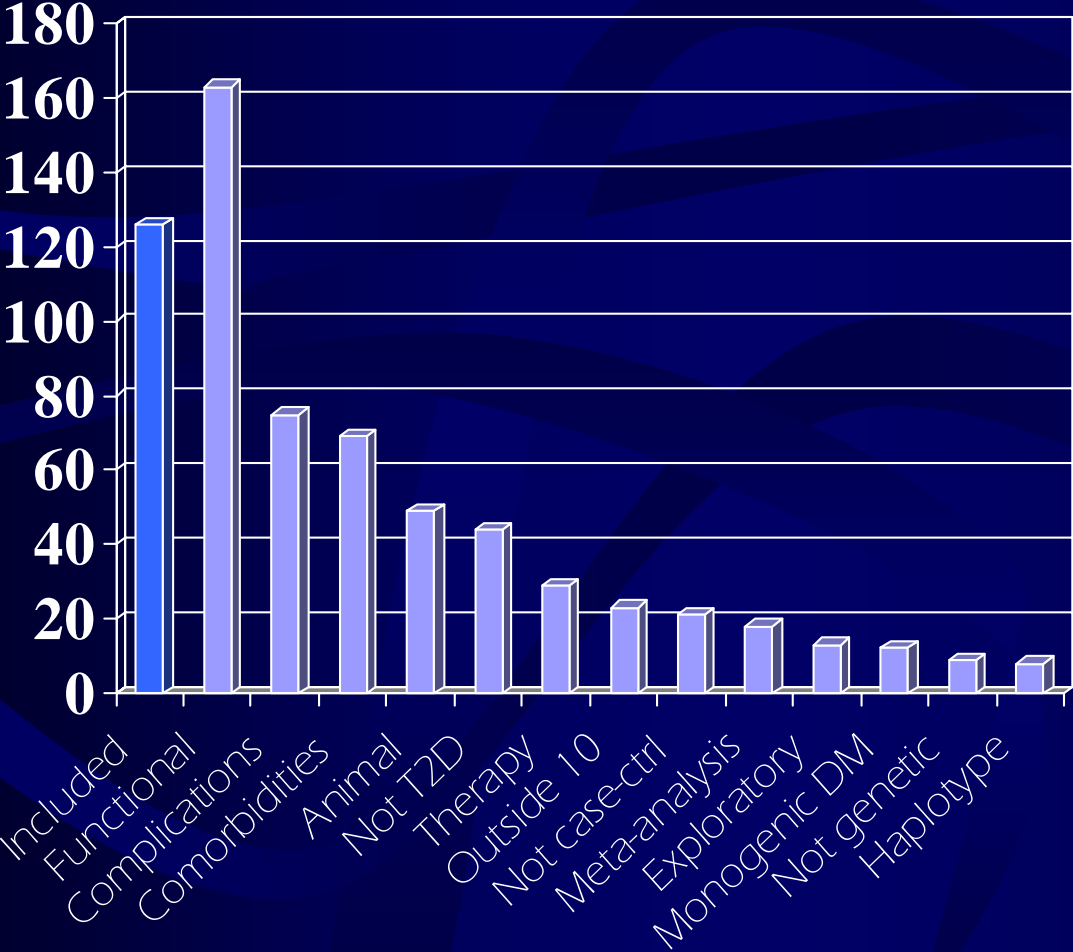
("diabetes mellitus, type 2/genetics"[Mesh Terms] NOT "diabetes mellitus, type 2/complications"[MAJR] AND (("ppar gamma"[MeSH Terms] OR PPAR gamma[Text Word]) OR "peroxisome proliferator-activated receptor gamma"[All Fields]) OR (Diabetologia AND (("ppar gamma"[MeSH Terms] OR PPAR gamma[Text Word]) OR "peroxisome proliferator-activated receptor gamma"[All Fields]) NOT "type 1 diabetes*"[TI]) NOT (PGC-1[All Fields] OR PGC1[All Fields] OR (ppargc1[All Fields] OR ppargc1a[All Fields] OR ppargc1a/b[All Fields] OR ppargc1b[All Fields]) NOT PPARGC1B[All Fields] OR "peroxisome proliferator-activated receptor gamma coactivator*"[All Fields]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR (("type 2 diabetes mellitus"[Text Word] OR "diabetes mellitus, type 2"[MeSH Terms] OR diabetes mellitus, type 2[Text Word]) AND TCF7L2[All Fields] OR (Diabetologia[All Fields] AND TCF7L2[All Fields] NOT "type 1 diabetes*"[TI]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR ("diabetes mellitus, type 2/genetics"[Mesh Terms] NOT "diabetes mellitus, type 2/complications"[MAJR] AND (ACE[All Fields] OR ("peptidyl-dipeptidase a"[MeSH Terms] OR angiotensin I converting enzyme[Text Word])) AND ("genetic markers"[MeSH Terms] OR "polymorphism, genetic"[MeSH Terms] OR "genetic predisposition to disease"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms]) OR (Diabetologia[All Fields] AND (ACE[All Fields] OR ("peptidyl-dipeptidase a"[MeSH Terms] OR angiotensin I converting enzyme[Text Word]) NOT "type 1 diabetes*"[TI]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR (("type 2 diabetes mellitus"[Text Word] OR "diabetes mellitus, type 2"[MeSH Terms] OR diabetes mellitus, type 2[Text Word]) AND (CAPN10[All Fields] OR ("calpain 10"[Substance Name] OR calpain-10[Text Word])) OR (Diabetologia[All Fields] AND (CAPN10[All Fields] OR ("calpain 10"[Substance Name] OR calpain-10[Text Word])) NOT "type 1 diabetes*"[TI]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR (("type 2 diabetes mellitus"[Text Word] OR "diabetes mellitus, type 2"[MeSH Terms] OR diabetes mellitus, type 2[Text Word]) AND (KCNJ11[All Fields] OR Kir6.2[All Fields]) OR (Diabetologia AND (KCNJ11[All Fields] OR Kir6.2[All Fields]) NOT "type 1 diabetes*"[TI]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR ("diabetes mellitus, type 2/genetics"[Mesh Terms] NOT "diabetes mellitus, type 2/complications"[MAJR] AND (HNF1[All Fields] OR TCF1[All Fields] OR "hepatocyte nuclear factor 1"[All Fields]) AND ("genetic markers"[MeSH Terms] OR "polymorphism, genetic"[MeSH Terms] OR "genetic predisposition to disease"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms]) OR (Diabetologia AND (HNF1[All Fields] OR TCF1[All Fields] OR "hepatocyte nuclear factor 1"[All Fields]) NOT "type 1 diabetes*"[TI]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR ("type 2 diabetes mellitus"[Text Word] OR "diabetes mellitus, type 2"[MeSH Terms] OR diabetes mellitus, type 2[Text Word]) AND (PGC-1[All Fields] OR (ppargc1[All Fields] OR ppargc1a[All Fields] OR ppargc1a/b[All Fields] OR ppargc1b[All Fields]) NOT PPARGC1B[All Fields] OR "peroxisome proliferator-activated receptor gamma coactivator*"[All Fields]) OR (Diabetologia[All Fields] AND (PGC-1[All Fields] OR (ppargc1[All Fields] OR ppargc1a[All Fields] OR ppargc1a/b[All Fields] OR ppargc1b[All Fields]) NOT PPARGC1B[All Fields]) NOT "type 1 diabetes*"[TI]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR (diabetes mellitus, type 2/genetics[MeSH] NOT diabetes mellitus, type 2/complications[MAJR] AND (HNF4[All Fields] OR ("hepatocyte nuclear factor 4"[MeSH Terms] OR hepatocyte nuclear factor 4[Text Word])) AND ("genetic markers"[MeSH Terms] OR "polymorphism, genetic"[MeSH Terms] OR "genetic predisposition to disease"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms]) OR (Diabetologia AND (HNF4[All Fields] OR ("hepatocyte nuclear factor 4"[MeSH Terms] OR hepatocyte nuclear factor 4[Text Word])) NOT "type 1 diabetes*"[TI]) AND (English[lang] AND hasabstract[text] NOT review[PT] NOT ("mice"[TIAB] NOT Medline[SB]) NOT ("rats"[TIAB] NOT Medline[SB])))) OR (diabetes mellitus, type 2/genetics[MeSH] NOT diabetes mellitus, type 2/complications[MAJR] AND (IL6[All Fields] OR ("interleukin-6"[MeSH Terms])) AND ("genetic markers"[MeSH Terms] OR "polymorphism, genetic"[MeSH Terms] OR "genetic predisposition to disease"[MeSH Terms] OR "epidemiologic studies"[MeSH Terms]) OR (Diabetologia AND (IL6[All 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Step 2 search results

Gene name	No. of articles
PPAR gamma	25
TCF7L2	23
CAPN10	20
KCNJ11	17
ABCC8 (SUR1)	11
ACE	9
HNF1 alpha (MODY3, TCF1)	14
HNF4 alpha (MODY4)	22
IL-6	9
PGC-1 alpha	9



Inclusion/exclusion



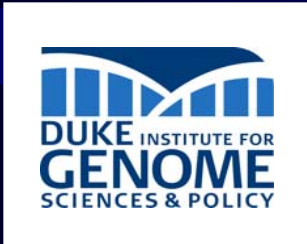
- Included
- Functional
- Complications
- Comorbidities
- Animal
- Not T2D
- Therapy
- Outside 10
- Not case-ctrl
- Meta-analysis
- Exploratory
- Monogenic DM
- Not genetic
- Haplotype

Database

1	A	C	G	H	I	J	AR	AS	AT	AU	AV	AV	AX	AY	AZ	BA	BB	BC	BD	BE
Arbitrary Info			Marker Data			Results														
Article #	Reader	SNP #	SNP name	Common name	Gene (if known)	Subgroup	Reference genotype	Counts for reference genotype	Overall prevalence of reference genotype	Reference risk	Risk (minor) allele	Counts for presence of risk allele	Overall risk allele frequency (total # of copies / (2 * sample size))	Counts for one copy (ie. heterozygous) risk genotype	Overall prevalence of one copy	Risk w/ one copy or allele				
							cases		controls				cases		controls		cases		controls	
70	136	AC	1	rs7903146		TCF7L2	NA	NA	NA	NA	1	T	NA	NA	0.26	NA	NA	NA	1.38	
72	2	AC	1	rs7903146		TCF7L2	V	CC	0.49	1	T		0.30		0.42	1.72				
73	2	AC	2	rs7903146		TCF7L2	B	CC	0.50	1	T		0.30		0.41	1.05				
74	5	EJ	1	rs7903146		TCF7L2	male	CC	0.48	1	T		0.31		0.43	1.22				
75	31	EJ	1	rs7903146		TCF7L2	all CC	C	not stated	1	T		not stated		not stated	1.39				
76	37	EJ	1	rs7903146		TCF7L2	NA	CC	771	1175	0.41	1	T		0.32	960	1084	0.43	1.35	
77	37	EJ	1	rs7903146		TCF7L2	NA				1	T							1.36	
78	20	EJ	1	rs1801282	Prot2Ala	PPAR gamma	age	Pro			0.87	1	C			0.13			0.13	1.12
79	7	EJ	3	rs1801282	Prot2Ala	PPAR gamma	DGI	C	NA	NA	NA	1	C	NA	NA	NA	NA	NA	NA	1.09
80	7	EJ	3	rs1801282	Prot2Ala	PPAR gamma	FUSION	C	NA	NA	NA	1	C	NA	NA	NA	NA	NA	NA	1.20
81	8	EJ	1	rs1801282	Prot2Ala	PPAR gamma	none	G	NA	NA	NA	1	C	NA	NA	82	NA	NA	NA	1.20
82	20	EJ	1	rs1801282	Prot2Ala	PPAR gamma	NA	Pro			0.87	1			0.13				0.13	
83	21	EJ	1	rs1801282	Prot2Ala	PPAR gamma	NA	C			0.16	1	C		0.84					1.30
84	33	EJ	2	rs1801282	Prot2Ala	PPAR gamma	NA	Pro	not stated	1	C		not stated		not stated				not stated	1.29
85	39	EJ	1	rs1801282	Prot2Ala	PPAR gamma	NA	Pro			0.16	1	G							0.30
86	62	AC	2	rs1801282	Prot2Ala	PPAR gamma	NA	PP	0.75	1	C		0.14						0.23	1.07
87	62	AC	2	rs1801282	Prot2Ala	PPAR gamma	NA	PP	0.75	1	C		0.14						0.23	1.05
88	89	AC	11	rs1801282	Prot2Ala	PPAR gamma	NA	CC	0.80	1	C		0.11						0.19	1.08
89	136	AC	3	rs1801282	Prot2Ala	PPAR gamma	NA	NA	NA	NA	1	C	NA	NA	0.86	NA	NA	NA	NA	1.09
90	20	EJ	1	rs1801282	Prot2Ala	PPAR gamma	triglyceride	Pro			0.87	1	C		0.13				0.13	1.51
91	52	AC	2	rs192673	Gly482Ser	PGC-1 alpha	NA	Gly/Gly			0.54	1	Ser		0.28				0.36	NA
92	6	EJ	2	rs192673	Gly482Ser	PGC-1 alpha	group 1	GG			0.44	1	A		0.34				0.44	2.17
93	6	EJ	2	rs192673	Gly482Ser	PGC-1 alpha	group 2	GG			0.52	1	A		0.28				0.40	1.51
94	12	EJ	1	rs192673	Gly482Ser	PGC-1 alpha	PPARG	Gly	not stated	1.1	Ser		not stated		not stated				0.91	
95	6	EJ	2	rs192673	Gly482Ser	PGC-1 alpha	NA	GG	0.48	1	A		0.31		0.42				1.82	
96	12	EJ	1	rs192673	Gly482Ser	PGC-1 alpha	NA	Gly	not stated	105			not stated		not stated				not stated	0.95
97	28	EJ	1	rs192673	Gly482Ser	PGC-1 alpha	NA	Gly	122	181	0.33	1	Ser	434	618	0.43	190	256	0.49	1.00
98	86	AC	1	rs192673	Gly482Ser	PGC-1 alpha	NA	GG	0.47	1	A		0.31		0.44				1.00	
99	89	AC	2	rs192673	Gly482Ser	PGC-1 alpha	NA	GG	0.43	1	A		0.35		0.43				1.00	
100	28	EJ	1	rs192673	Gly482Ser	PGC-1 alpha	M	Gly	53	105	0.33	1	Ser	346	432	0.44	93	126	0.46	1.85
101	108	EJ	1	rs192673	Gly482Ser	PGC-1 alpha	NA	Gly/Gly	262	243	0.43	1	Ser	297	196	0.21			0.00	
102	17	EJ	1	rs5219	E23K	KCNJ11	NA					1								
103	113	AC	1	rs5219	E23K	KCNJ11	NA	GG	133	125	0.39	1	A	293	106	0.30	161	152	0.47	NA

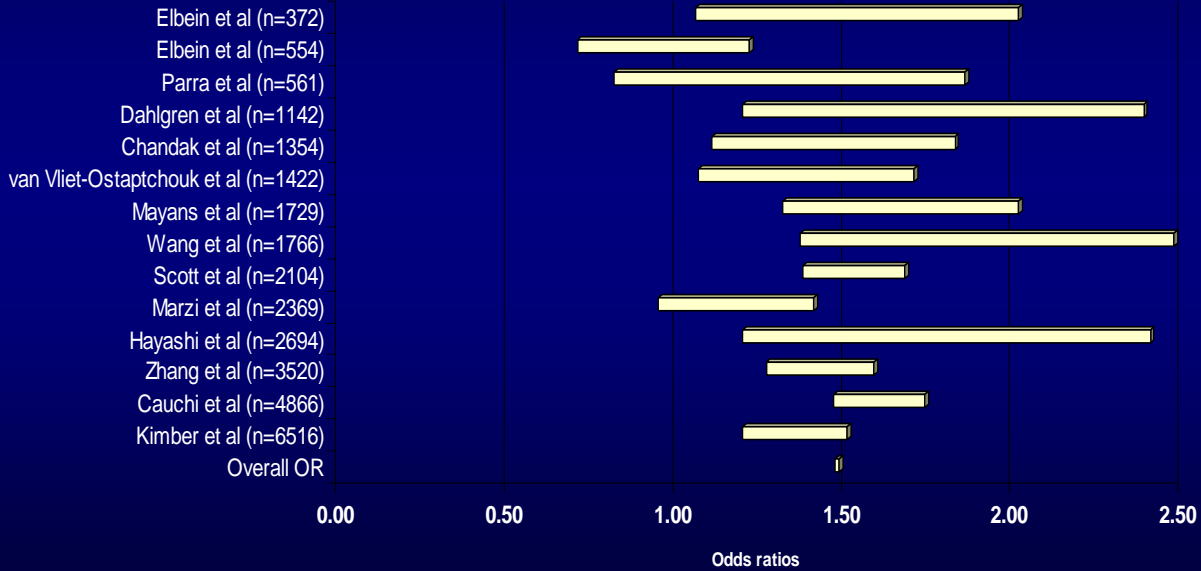
Key Polymorphisms

Polymorphism	Alias	Risk Allele	# Studies	# Sig positive result*	Ratio	Overall OR	Range of 95% CIs
rs7903146		T	21	17	0.810	1.42	0.80-2.67
rs12255372		T	17	12	0.706	1.45	0.71-2.88
rs1801282	Pro12Ala	C (Pro)	19	9	0.474	1.33	0.69-278
rs5219	E23K	A (Lys)	15	8	0.533	1.24	0.67-3.59
rs3792267	SNP-43	A	13	1	0.077	1.08	0.87-1.30
rs1884613		G	10	1	0.100		
rs1885088		A	8	0	0.000		
rs2144908		A	10	1	0.100		
rs2425637		T	8	1	0.125		
rs3818247		T	8	1	0.125		
rs1169288	I27L	G	2	1	0.500		
rs8192673	Gly482Ser	A	7	2	0.286	1.26	0.77-2.42
rs1800795	C-174G	G	7	2	0.286	1.60	0.90-2.30
	I/D	del	8	3	0.375	1.09	0.46-2.26
rs757110	Arg1273Arg	G	3	2	0.667	1.54	0.96-5.99



rs12255372 (TCF7L2)

Plot of ORs for risk of T2D w/ rs12255372 (TCF7L2)



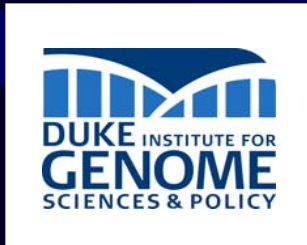


Preliminary Results

- **Single nucleotide polymorphisms (SNPs) in TCF7L2, PPAR gamma 2, and KCNJ11 appeared to be validated multiple times, with average ORs ranging from 1.24 to 1.45.**
- **Increased risk associated with these polymorphisms may be comparable to that for increased BMI (HR ~ 1.25/100-person-years) but less than that associated with a positive family history of diabetes (OR ~ 3.5).**
- **However, genomic testing for risk of Type 2 diabetes may be helpful in patients who lack these traditional risk factors.**
- **Other promising SNPs found by recent genome-wide association studies await validation in multiple studies.**

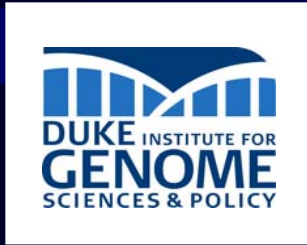
Emerging SNPs

rs	chr	position	A1	A2	Region	WTCCC	P_{add}	Replication	P_{add}	All UK sample	P_{add}	DGI	P_{add}	FUSION	P_{add}	All combined	P_{add}
						1924 cases 2938 controls OR (95% CI)		meta-analysis 3757 cases 5345 controls OR (95% CI)		meta-analysis 5681 cases 8284 controls OR (95% CI)		6529 cases 7252 controls OR (95% CI)		2376 cases 2432 controls OR (95% CI)		14,586 cases 17,968 controls OR (95% CI)	
rs9050136	16	52373776	A	C	FTO	1.27 (1.16–1.37)	2.0×10^{-8}	1.22 (1.12–1.32)	5.4×10^{-7}	1.23 (1.18–1.32)	7.3×10^{-14}	1.03 (0.91–1.17)	0.25	1.11 (1.02–1.20)	0.017	1.17 (1.12–1.22)	1.3×10^{-12}
rs10946398	6	20769013	A	G	CDKN11	1.20 (1.10–1.31)	2.5×10^{-5}	1.14 (1.07–1.22)	8.3×10^{-5}	1.16 (1.10–1.22)	1.3×10^{-8}	1.08 (1.03–1.14)	2.4×10^{-2}	1.12 (1.03–1.22)	9.5×10^{-2}	1.12 (1.09–1.16)	4.1×10^{-11}
rs5015480	10	94455539	G	T	HNEK	1.22 (1.12–1.32)	5.4×10^{-6}	–	–	1.13 (1.07–1.19)	4.6×10^{-6}	1.14 (1.06–1.22)	1.7×10^{-4}	1.10 (1.01–1.19)	0.025	1.13 (1.09–1.17)	5.7×10^{-10}
rs1111875	10	94452862	C	T	HNEK	–	–	1.08 (1.01–1.15)	0.020	–	–	–	–	–	–	–	–
rs10811661	9	22124094	G	T	CDKN2B	1.22 (1.09–1.37)	7.6×10^{-4}	1.18 (1.09–1.28)	1.7×10^{-4}	1.19 (1.11–1.28)	4.9×10^{-7}	1.20 (1.12–1.28)	5.4×10^{-8}	1.20 (1.07–1.36)	2.2×10^{-2}	1.20 (1.14–1.25)	7.8×10^{-15}
rs564398	9	22019547	C	T	CDKN2B	1.16 (1.07–1.27)	3.2×10^{-4}	1.12 (1.05–1.19)	8.6×10^{-4}	1.13 (1.09–1.19)	1.3×10^{-6}	1.05 (0.94–1.17)	0.5	1.13 (1.01–1.27)	0.039	1.12 (1.07–1.17)	1.2×10^{-7}
rs4402960	3	186994399	G	T	KGF2BP2	1.15 (1.05–1.25)	1.7×10^{-2}	1.09 (1.01–1.16)	0.018	1.11 (1.05–1.16)	1.6×10^{-4}	1.17 (1.11–1.23)	1.7×10^{-9}	1.18 (1.09–1.28)	2.4×10^{-4}	1.14 (1.11–1.18)	8.6×10^{-16}
rs13266624	8	118253964	G	T	SLC30A8	1.12 (1.02–1.22)	0.020	1.12 (1.04–1.19)	1.2×10^{-2}	1.12 (1.05–1.18)	7.0×10^{-5}	1.07 (1.00–1.16)	0.047	1.18 (1.09–1.29)	7.0×10^{-5}	1.12 (1.07–1.16)	5.3×10^{-8}
rs7901695	10	114744078	G	T	TCF7L2	1.37 (1.25–1.49)	6.7×10^{-12}	–	–	–	–	1.38 (1.31–1.46)	2.3×10^{-21}	1.34 (1.21–1.49)	1.4×10^{-8}	1.37 (1.31–1.43)	1.0×10^{-48}
rs5215	11	17365206	C	T	KCNJ11	1.15 (1.05–1.25)	1.3×10^{-2}	–	–	–	–	1.15 (1.09–1.21)	1.0×10^{-7}	1.11 (1.02–1.20)	0.014	1.14 (1.10–1.19)	5.0×10^{-11}
rs1801282	3	12368125	G	C	PPARG	1.23 (1.09–1.41)	1.3×10^{-2}	–	–	–	–	1.09 (1.01–1.16)	0.019	1.20 (1.07–1.33)	1.4×10^{-2}	1.14 (1.09–1.20)	1.7×10^{-6}



Choosing Message

- **Stress 'sensitivity' of testing, but downplay 'specificity'**
 - i.e., results can really only tell if at higher risk
- **Avoid overselling**
- **General risk assignment**
 - High, Intermediate, Baseline
 - Along with BMI, FH, FPG
- **Numbers for individual markers**
- **Recommended action(s) plus tools**
- **'Dossier' of supporting evidence**

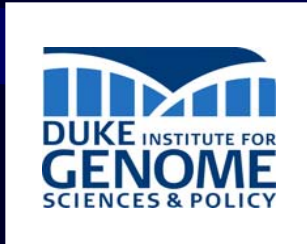


Choosing Message

	Copy 1	Copy 2
<i>TCF7L2</i>		
<i>KCNJ11</i>		
<i>PPAR gamma 2</i>	■	■

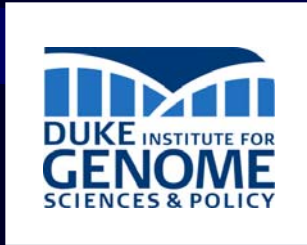
	Copy 1	Copy 2
<i>TCF7L2</i>	■	
<i>KCNJ11</i>	■	
<i>PPAR gamma 2</i>	■	■

Figure 2. Sample 2x3 matrices. Colored box = positive for one copy of higher-risk allele. Matrix on the left depicts 'average risk' case, for comparison. This individual has one copy of the higher-risk allele for *TCF7L2* and *KCNJ11*, and two copies of the more common higher-risk allele for *PPAR gamma 2*.

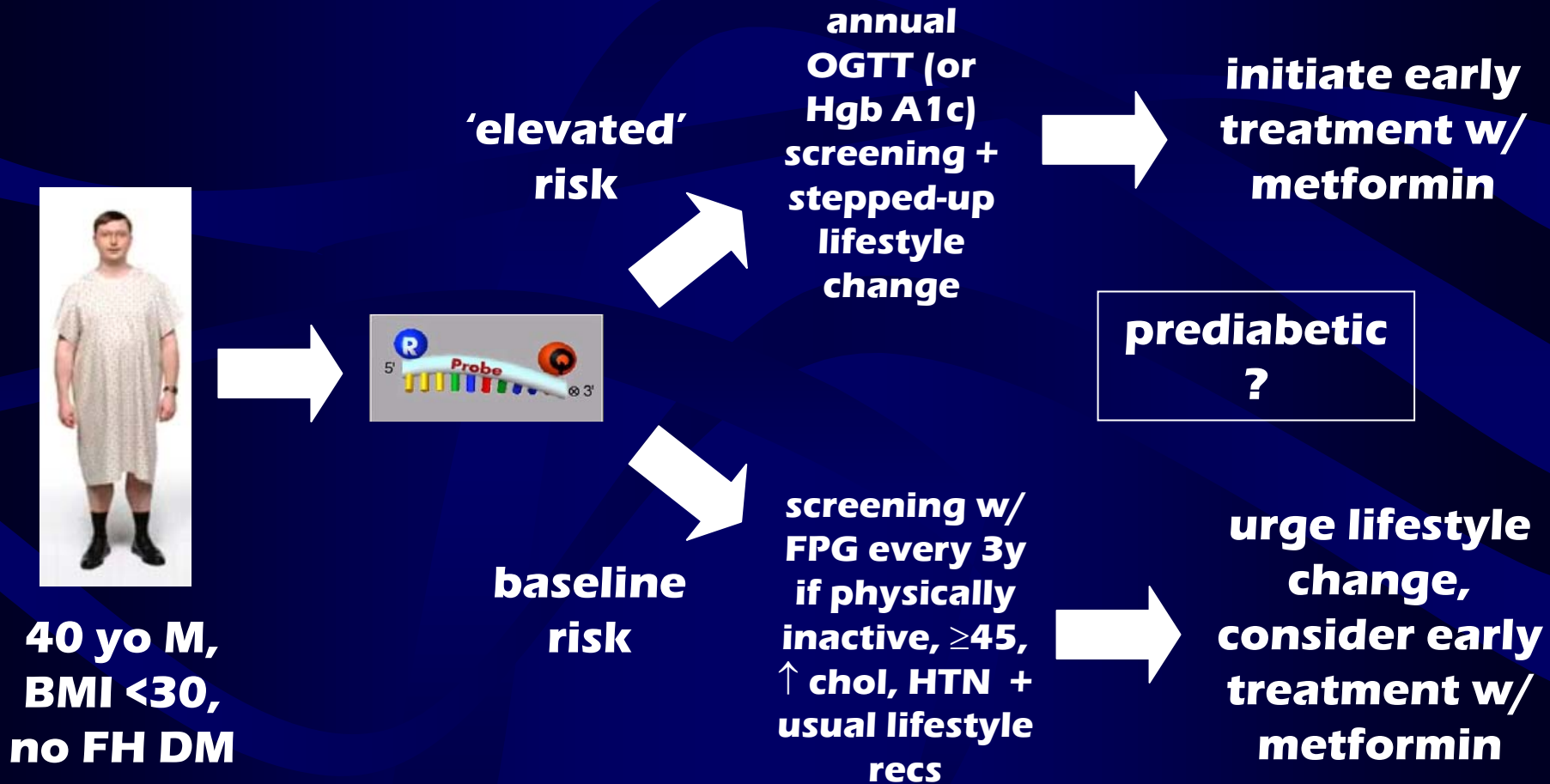


Clinical Utility

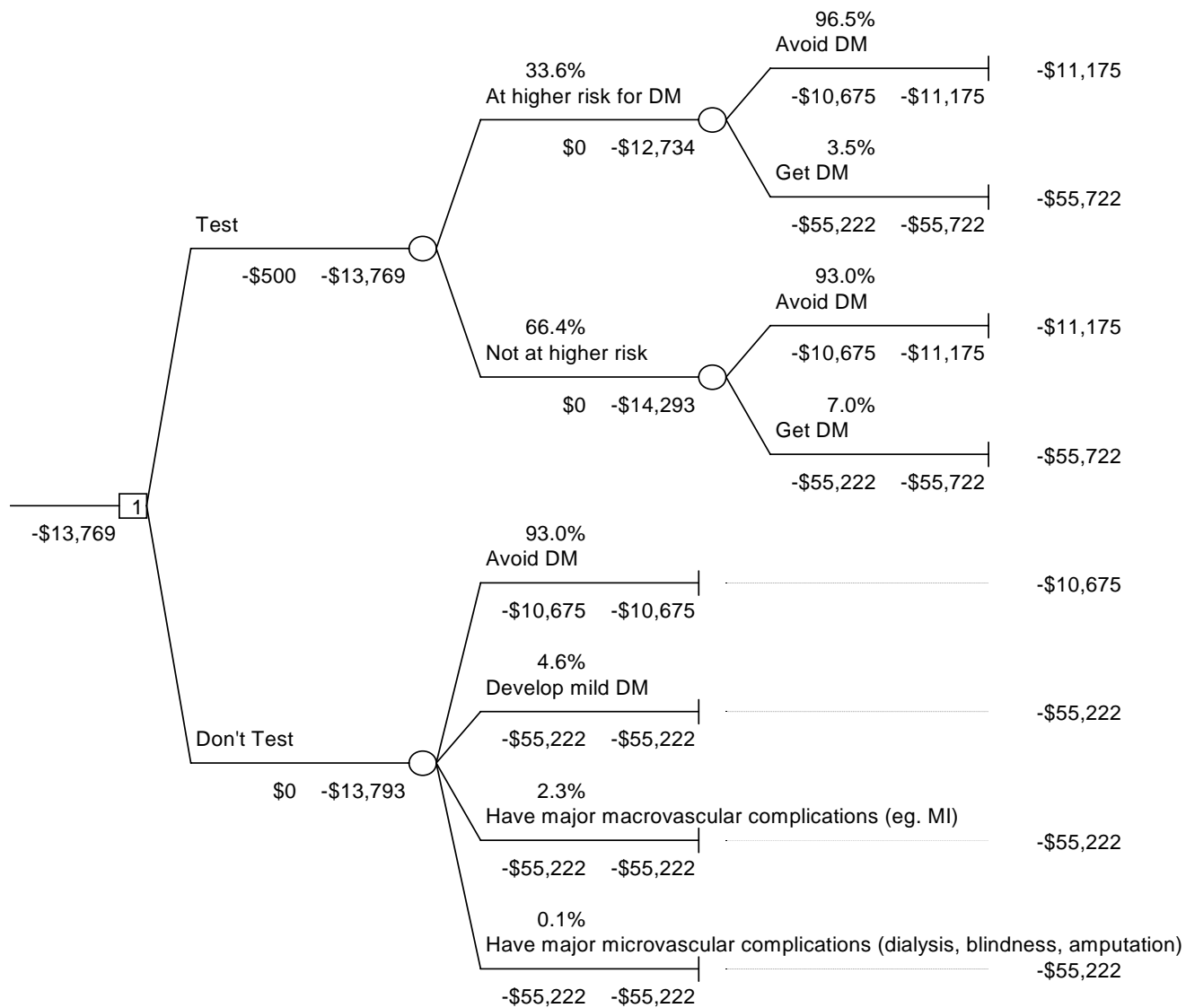
- **Demonstrating clinical utility**
 - **Role in care**
 - **Modeling**
 - **Studies**
 - **Observational studies**
 - **RCTs**



Place of DNA testing in diabetes risk assessment

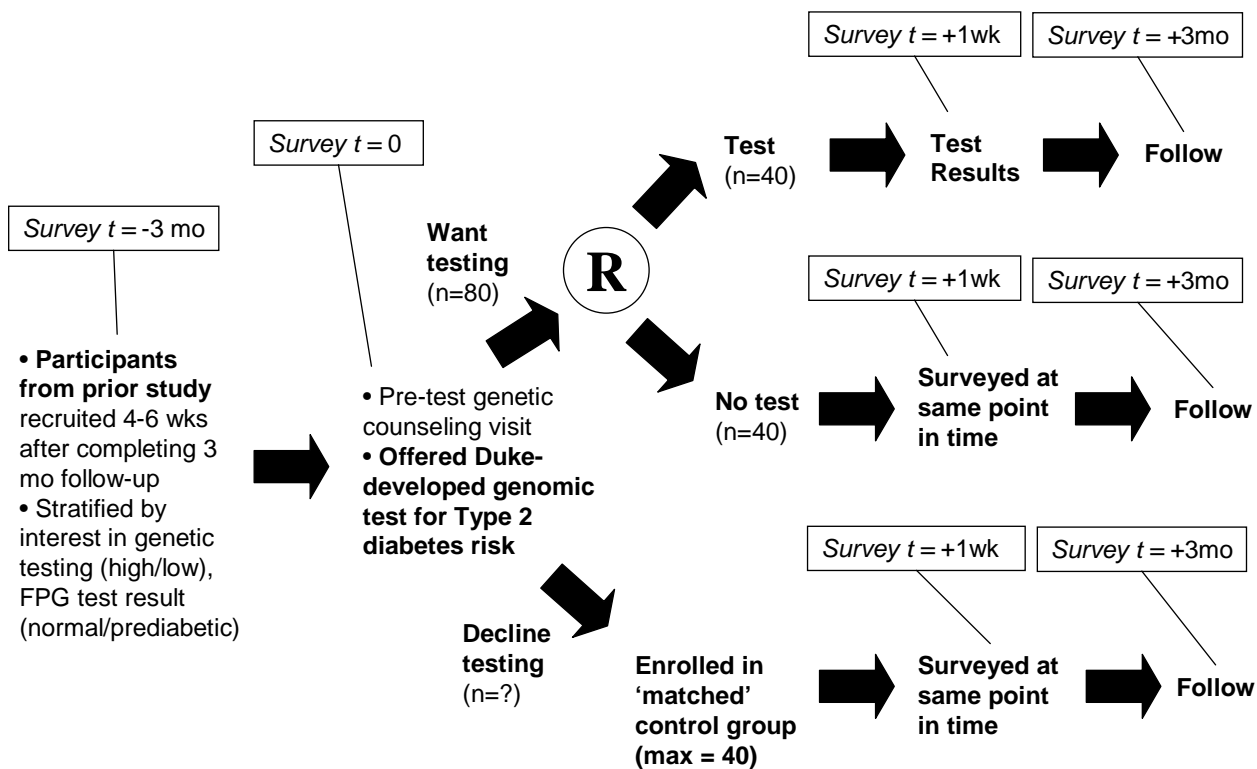


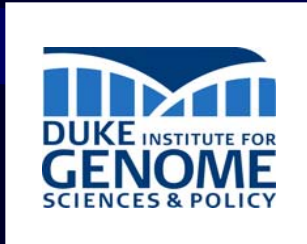
OGTT = oral glucose tolerance testing, FPG = fasting plasma glucose



A Proposed Study

Figure. Research Design





Externalities

- **Genetic discrimination**
- **Mistaken labeling as diabetic**
- **Licensing of patented markers**

Externalities

United States Patent Application

20060286588

Kind Code

A1

Grant; Struan F.A.

December 21, 2006

Genetic variants in the *TCF7L2* gene as diagnostic markers for risk of type 2 diabetes mellitus

Abstract

Polymorphisms in the gene *TCF7L2* are shown by association analysis to be a susceptibility gene for type II diabetes. Methods of diagnosis of susceptibility to diabetes, of decreased susceptibility to diabetes and protection against diabetes, are described, as are methods of treatment for type II diabetes.

Inventors: **Grant; Struan F.A.**; (*Reykjavik, IS*)

Correspondence **HAMILTON, BROOK, SMITH & REYNOLDS, P.C.**

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Serial No.: **454296**

Series Code: **11**

Filed: **June 16, 2006**

U.S. Current Class:

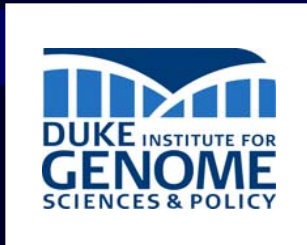
435/6

U.S. Class at Publication:

435/006

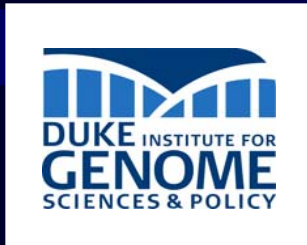
Intern'l Class:

C12Q 1/68 20060101 C12Q001/68



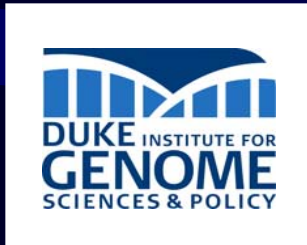
Duke Executive Health

- **Response to patient demand**
 - **88% of Duke Executive Health clients surveyed want genetic testing**
- **Target population**
 - 1. Worried well, usually b/c +FH**
 - 2. Those who want cutting-edge technology**
 - 3. Intermediate risk patients who could benefit from additional information**
- **Proposed familial genetic assessment service also in works (Julianne O'Daniel)**



Duke Executive Health

- **Everyone receives FPG screening**
- **MD uses clinical data to underline importance of lifestyle change, other**
- **Nutrition most likely to tailor to clinical**
- **Most do not go through exercise, nutrition, stress management on return visits**
 - **Suggests missed opportunity for reinforcement**
- **Patients get a great deal of information in a relatively brief span of time**
 - **Also delivered in written form**



Duke Executive Health

– Before the visit

• Intake

- Patient selects 'DNA testing' under Optional Tests
- Provides family history

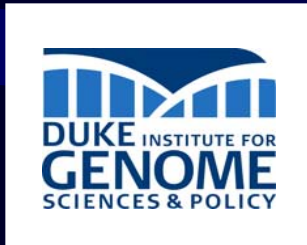
- Advance contact is made to do pre-test counseling, arrange for sample collection

– At the visit

- Tests ordered may change due to results (eg. OGTT)
- Nutrition can tailor session accordingly
- Results are presented to patient by Exec Health MD, along with supporting documentation

– After the visit

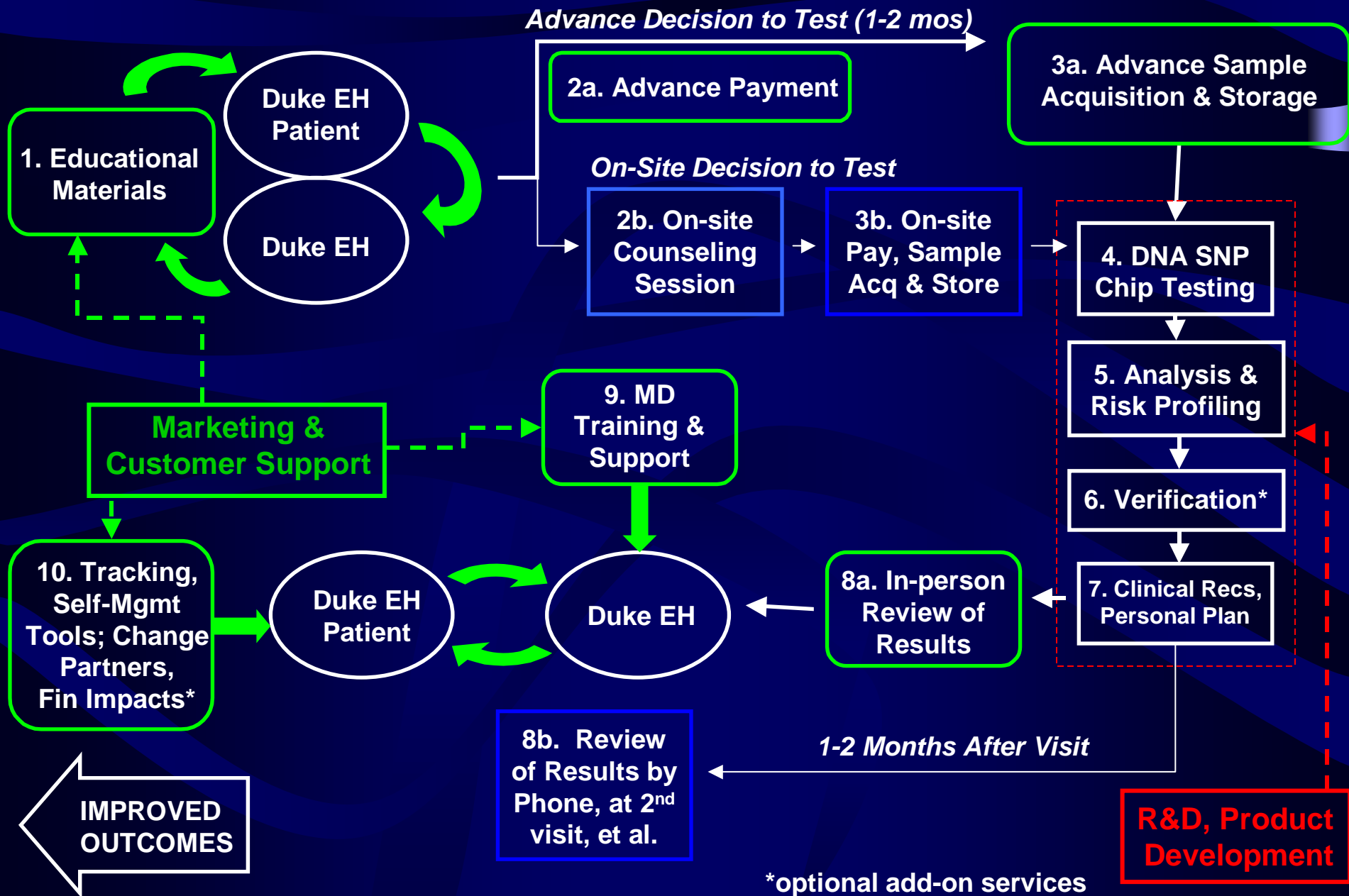
- Adherence to goals tracked, re-visited at future visits

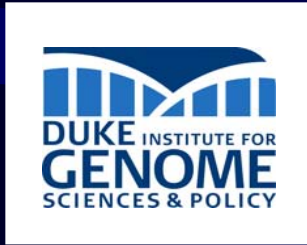


The individualized risk profile (*irp*)

- **Intake (demographics, health and family history)**
- **Pre-test counseling**
- **Sample acquisition**
- **Testing for condition of interest**
- **Delivery of test results and explanation**
- **Strategic health action planning and execution (SHAPE)
 - **Goal-setting exercises**
 - **Tracking, referral to change partners****
- **Dossier for condition of interest**

Proposed Testing Process (Duke EH)





Future Directions

- **Continue Type 2 diabetes work**
- **Age-related macular degeneration**
- **Breast cancer**
- **Anticoagulation**
- **Prostate cancer**
- **Other clinical opportunities**
- **Critical appraisal unit?**



Discussion
