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Chapter 1

NA

Chapter 2

Table 1: PharmGKB 'Very Important Pharmacogenes' as of 2020

Gene	Gene product	Drug(s)	Overview of guideline (s)

ABCB1	P-glycoprotein (P-gp)	Many, including: anti-depressants, anti-virals, chemotherapeutics, opioids, steroids,	Encodes a transporter protein, which effluxes many substrates. This leads to a number of drug-drug interactions (e.g. rifampin and contraceptives) that can reduce efficacy. Also responsible for drug resistance in some cancers (1).
ABCG2	BCRP transporter protein	Many, including: anti-virals, chemotherapeutics, anti-fungals	Encodes a transporter protein, similar to P-gp. Leads to a number of drug-drug interactions (e.g. pitavastatin and cyclosporin), and can reduce efficacy. Responsible for drug resistance in some cancers (2).
ACE	ACE enzyme	ACE inhibitors, statins	Contradictory reports on the effect of *ACE* variants on ACE inhibitor response, but most focus on just one variant so further variant testing required (3).
ADRB1	Beta-1-adrenergic receptor	Anti-hypertensives, beta-blockers	The beta-1-adrenergic receptor mediates heart rate and contractility. Variants affect the efficacy of drugs treating hypertension, coronary artery disease, and heart failure (4, 5).
ADRB2	Beta-2-adrenergic receptor	Anti-hypertensives, beta-blockers	This receptor is expressed in cardiac myocytes and in bronchial and vascular smooth muscle cells. Variants affect the efficacy of drugs treating hypertension, congestive heart failure, and asthma (6).
CACNA1S	Dihydropyridine receptor (DHPR) [alpha subunit]	Volatile anaesthetics	DHPR is a voltage-gated calcium channel in skeletal muscle. Variants are linked to malignant hyperthemia susceptibility and hypokalaemic periodic paralysis (7).
CFTR	CFTR protein	Ivacaftor	Variants in *CFTR* cause cystic fibrosis. Over 1800 variants have been reported. Ivacaftor targets several specific *CFTR* variants, responsible for 4-5% of cystic fibrosis cases (8).
COMT	Catechol-O-methyltransferase	Many, including: anti-psychotics, drugs for management of Parkinson's disease, opioids,	Variants in *COMT* are associated with requiring higher doses of drugs in schizophrenia and higher doses of morphine in pain (9).
CYP2A6	CYP2A6 enzyme	Many, including: anti-virals, chemotherapeutics, nicotine, steroids	Encodes an enzyme affects the metabolism of nicotine (polymorphisms are linked to smoking behaviours). Also has a key role in the metabolism of many other drugs (10).

CYP2B6	CYP2B6 enzyme	Many, including: anti-depressants, anti-virals, chemotherapeutics	Encodes an enzyme responsible for metabolism of 4% of the top 200 drugs. Variants are associated with increased risk of ADRs from cyclophosphamide, efavirenz, and bupropion (11).
CYP2C19	CYP2C19 enzyme	Many, including: anti-depressants, anti-platelet drugs, proton pump inhibitors	Encodes a liver enzyme with polymorphisms leading to reduced or absent enzyme activity. Loss-of-function mutations are associated with lower efficacy of several drugs (12).
CYP2C8	CYP2C8 enzyme	Many, including: anti-diabetics, chemotherapeutics, opioids, statins	Encodes a liver enzyme that metabolises several large compounds. Has many polymorphisms associated with variability in drug response (13).
CYP2C9	CYP2C9 enzyme	Many, including: anticoagulants, chemotherapeutics, NSAIDs, statins	Encodes a liver enzyme responsible for metabolic clearance of 15-20% of drugs. This leads to drug-drug interactions, reduced efficacy, or increased risk of ADRs, depending on the variant and the drug (14).
CYP2D6	CYP2D6 enzyme	Many, including: anti-depressants, anti-hypertensives, chemotherapeutics, opioids	Encodes a liver enzyme involved in metabolism of up to 25% of commonly-used drugs. Leads to drug-drug interactions, reduced efficacy, or increased risk of ADRs, depending on the variant and the drug (15).
CYP3A4	CYP3A4 enzyme	Many, including: anti-platelet drugs, chemotherapeutics, antibiotics	Encodes an enzyme that is responsible for metabolism of 40-50% of drugs in use. Different polymorphisms responsible for variability in response to many drugs (16).
CYP3A5	CYP3A5 enzyme	Many, including: anti-virals, benzodiazepines, chemotherapeutics	Encodes an enzyme responsible for metabolism of many common drugs. Different polymorphisms responsible for variability in response to many drugs (17).
CYP4F2	CYP4F2 enzyme	Vitamins E and K, anti-parasitic drugs	Encodes an enzyme that metabolises many endogenous compounds, affecting the dosing of warfarin (18).
DPYD	DPYD enzyme	Fluoropyrimidines	Polymorphisms that lead to decreased DPYD activity increase the risk of toxicity from standard doses of fluoropyrimidine drugs (e.g. 5-fluorouracil, capecitabine) (19).

DRD2	Dopamine receptor D2	Anti-parkinsonian medications, anti-psychotics	Many drugs for Parkinson's disease use this receptor. More research has been done on the link between variants and response to anti-psychotic drugs (20).
F5	Factor V coagulation factor	Oral contraceptives	There is a well-established link between the Factor V Leiden polymorphism and VTE. Users of oral contraceptives with this polymorphism have a higher risk of VTE than wild-type users (21).
G6PD	G6PD enzyme	Anti-diabetes drugs, anti-malarials, chemotherapeutics	G6PD deficiency was one of the first mechanisms found to be linked to variable drug response. G6PD-deficient individuals are at higher risk of adverse drug reactions in response to several triggers, including some drugs (22).
GSTP1	GSTP1 isoform of GST enzyme	Chemotherapeutics, particularly platinum agents	The rs1695 polymorphism is associated with reduced enzyme activity, causing drug resistance and toxicity (23).
HLA-B	HLA-B cell surface molecule	Abacavir, allopurinol, carbamazepine, flucloxacillin, phenytoin	Strongly associated with several ADRs, particularly SJS/TEN in response to carbamazepine and phenytoin. Testing is strongly recommended by several agencies (24).
MTHFR	MTHFR enzyme	Chemotherapeutics and anti-rheumatic drugs	Increased risk of methotrexate toxicity with rs1801131 polymorphism. Also linked to survival in 5-fluorouracil-treated patients (25).
MT-RNR1	MT-RNR1 ribosomal RNA in mitochondria	Aminoglycoside antibiotics	The 1555A>G variation is strongly linked to hearing loss following aminoglycoside antibiotic use – 100% of aminoglycoside patients with the variant develop hearing loss (26).
NAT2	NAT2 enzyme	Many, including: antibiotics, anti-inflammatories, vasodilators	Variations in *NAT2* are linked to drug-induced hepatotoxicity with anti-TB drugs and ADRs with hydralazine treatment. Variations are also linked to patients requiring higher doses of sulfamethoxazole (27).
NUDT15 [MTH2]	NUDT15 enzyme	Thiopurine drugs	One variant (rs25108385) linked to toxicity from azathioprine and mercaptopurine (28).

RYR1	RYR1 calcium channel	Inhalational anaesthetics and depolarising muscle relaxants	'Dozens' of variants in *RYR1* increase the risk of malignant hyperthermia in response to anaesthesia (29).
SLC19A1	RFC1 transporter protein	Folic acid, vitamin B12, methotrexate	The GG genotype increases the risk of spina bifida in infants. Other variants are associated with an increased risk of methotrexate toxicities (30).
SLCO1B1	OATP1B1	Many, including: ACE inhibitors, antibiotics, chemotherapeutics, statins	OATP1B1 is an active transport protein, responsible for mediating drug hepatic clearance. Some phenotypes result in impaired hepatic access, reducing drug efficacy (31).
TPMT	TPMT	Thiopurine drugs (e.g. 6-mercaptopurine, azathioprine)	Encodes the TPMT enzyme that metabolises thiopurine drugs. Higher TPMT activity reduces efficacy of these drugs, lower activity increases the risk of ADRs (32).
TYMS	TYMS enzyme	5-fluorouracil, methotrexate	Over-expression is linked to fluorouracil resistance in cancers. Other variants are associated with better responses to chemotherapy (33).
UGT1A1	UGT1A1 enzyme	Irinotecan	The *28 and *6 alleles are associated with irinotecan toxicities, particularly neutropenia (34).
VKORC1	VKORC1 enzyme	Warfarin	Encodes a key enzyme in the vitamin K cycle. Vitamin K is a key component of coagulation factor proteins. Warfarin inhibits VKORC1, leading to a reduction in coagulation factor proteins. High and low dose variants of *VKORC1* have been found (35).

Table 1 - Very important pharmacogenes as designated by PharmGKB (www.pharmgkb.org) as of October 2020 (36, 37). ADR = adverse drug reaction. NSAIDs = non-steroidal anti-inflammatory drugs. SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis. TB = tuberculosis. VTE = venous thromboembolism.

Chapter 3

Table 2: Full data extraction of trials included in Chapter 3 biomarker review

Registration	Trial name	Start year	Year of results publication	References source	Trial design	Biomarker	Biomarker application	Drug of interest	Sample size (n randomised)	Age	Sex (% F/M)	Race	Location
ISRCTN30748308	TARGET (38, 39)	2005	2011	2005 protocol obtained from authors (39)	Biomarker strategy design (without biomarker assessment in control arm)	*TPMT*	Prevention of ADRs	Azathioprine	333	Mean 43.2 (non-genotyped)	50.6/49.4 (non-genotyped)	White/South Asian/Black/ mixed or other (non-genotyped)	UK
										Mean 41.0 (genotyped)	50.3/49.7 (genotyped)	White/South Asian/Black (genotyped)	
NCT01119300	EU-PACT (40)	2011	2013	2009 protocol paper 10.2217/pgs.09.125	Biomarker strategy design (without biomarker assessment in control arm)	*CYP2C9*2 CYP2C9*3 VKORC1*	Improving efficacy	Warfarin	455	Mean 66.9 (control)	42.1/57.9 (control)	White/Black/ Asian (control)	UK Sweden
										Mean 67.8 (genotyped)	35.8/64.2 (genotyped)	White/Black/ Asian (genotyped)	
NCT01771458	SHIVA (41)	2012	2015	2014 protocol obtained from supplementary (41)	Enrichment design	Hormone receptors *PI3K/AKT/ mTOR RAF/MEK*	Targeted therapies	Targeted chemotherapy agents	195	Median 63 (control)	72/28 (control)	Not reported	France
										Median 61 (genotyped)	61/39 (genotyped)		
NCT01894230	GIST (42)	2013	2018	2016 rationale paper	Biomarker strategy design (with biomarker	*SLCO1B1* 5*	Improving adherence	Any statin	159	Mean 62.5 (control)	65.8/34.2 (control)	White/Black/ other	USA

				10.2217/pgs-2016-0065	assessment in control arm)					Mean 62.7 (genotyped)	49.4/50.6 (genotyped)	White/Black/ other	
NCT02664350	n/a (43)	2016	Results not yet published	2018 protocol paper 10.1016/ j.cct.2018.03.001	Biomarker strategy design (without biomarker assessment in control arm)	*CYP2D6*	Quality of life	Opioids	200 (forecast)	Not available	Not available	Not available	USA

Table 2: Full data extraction of the 5 randomised controlled trials included in Chapter 3 biomarker review.

Table 3: Full list of evidence cited by TARGET trial in biomarker review

No.	Type of reference	Authors	Year	DOI
1	Observational – cohort	Dubinsky et al (44)	2000	10.1016/S0016-5085(00)70140-5
2	Observational – cohort	Weinshilboum and Sladek(45)	1980	n/a
3	Observational – case control	Lennard et al(46)	1989	10.1038/clpt.1989.119
4	Observational – cohort	McLeod et al(47)	1994	10.1038/clpt.1994.4
5	Observational – cohort	Yates et al(48)	1997	10.7326/0003-4819-126-8-199704150-00003
6	Guidelines	British Society of Rheumatology [not found]	2000	n/a
7	Observational – of assay use	Holme et al(49)	2002	10.1093/qjmed/95.7.439
8	Observational – cohort	Bloomfeld & Onken (50)	2003	10.1046/j.1365-2036.2003.01392.x
9	Observational – cohort	McLeod et al (51)	1999	10.1046/j.1365-2141.1999.01416.x
10	Observational – cohort	Black et al (52)	1998	10.7326/0003-4819-129-9-199811010-00007
11	Observational – cohort	Pandya et al (53)	2002	10.1016/S0041-1345(02)02963-9
12	Expert opinion	Seidman(54)	2003	n/a

13	Observational – cohort	Murphy & Atherton (55)	2002	10.1046/j.1365-2133.2002.04922.x
14	Systematic review	Phillips et al	2001	10.1001/jama.286.18.2270
15	Case study	Tavadia et al(56)	2000	10.1067/mjd.2000.103980
16	Cost-effectiveness study	Marra et al (57)	2002	n/a
17	Qualitative work	Tan et al (58)	1997	10.1046/j.1365-2133.1997.d01-1198.x

Table 3 - evidence cited for biomarker inclusion by the TARGET randomised controlled trial. This is based on the 2005 protocol for TARGET (39)

Table 4: Full list of evidence cited by EU-PACT trial in biomarker review

No.	Type of reference	Authors	Year	DOI
1	Editorial	Rosendaal (59)	1996	10.1056/NEJM199608223350810
2	Observational – retrospective cohort ◆	James et al (60)	1992	n/a
3	Observational – cohort	Penning-van Beest et al (61)	2001	n/a
4	Observational – case control	Hylek et al (62)	1996	10.1056/NEJM199608223350802
5	Editorial	Pirmohamed (63)	2006	10.1111/j.1365-2125.2006.02806.x
6	Observational – case control	Penning-van Beest et al (64)	2002	10.1016/S0895-4356(01)00485-1
7	Observational – cohort	Carlquist et al (65)	2006	10.1007/s11239-006-9030-7
8	Observational – cohort	Schalekamp et al (66)	2007	10.1007/s00228-007-0268-6
9	Observational – case control	Schalekamp et al (67)	2008	10.1001/archinternmed.2007.32
10	Observational – cohort	Gage et al (68)	2004	10.1160/TH03-06-0379
11	Observational – cohort (healthy volunteers)	Bodin et al (69)	2005	10.1182/blood-2005-01-0341
12	Observational – cohort	Wadelius et al (70)	2009	10.1182/blood-2008-04-149070
13	Observational – cohort	Schalekamp et al (71)	2006	10.1016/j.clpt.2006.04.006
14	Observational – cohort	Schalekamp et al (72)	2007	10.1038/sj.clpt.6100036
15	Observational – case control	Reitsma et al (73)	2005	10.1371/journal.pmed.0020312
16	Observational – cohort	Wadelius et al (74)	2005	10.1038/sj.tpj.6500313
17	Observational – cohort	D'Andrea et al (75)	2005	10.1182/blood-2004-06-2111
18	Observational – cohort (GWAS)	Takeuchi et al (76)	2009	10.1371/journal.pgen.1000433

19	Observational – cohort	Caldwell et al (77)	2008	10.1182/blood-2007-11-122010
20	Observational – cohort	Schelleman et al (78)	2008	10.1038/clpt.2008.101
21	Observational – cohort	Klein et al (79)	2009	10.1056/NEJMoa0809329.
22	Observational – cohort	Perini et al (80)	2008	10.1038/clpt.2008.166
23	Observational – cohort	Sconce et al (81)	2005	10.1182/blood-2005-03-1108
24	Observational – cohort	Tham et al (82)	2006	10.1016/j.clpt.2006.06.009
25	Observational – cohort	Gage et al (83)	2008	10.1038/clpt.2008.10
26	Cost-effectiveness analysis	Eckman et al (84)	2009	10.7326/0003-4819-150-2-200901200-00005
27	Cost-effectiveness analysis	Schalekamp et al (85)	2006	10.1016/j.clpt.2006.03.008
28	Literature review	Hughes and Pirmohamed (86)	2007	10.2165/00019053-200725110-00001

Table 4- evidence cited for biomarker inclusion by the EU-PACT randomised controlled trial. Based on 2009 protocol for EU-PACT (40).

Table 5: Full list of evidence cited by SHIVA trial in biomarker review

No.	Type of reference	Authors	Year	DOI
1	Randomised controlled trial	Slamon et al (87)	2001	10.1056/NEJM200103153441101
2	Observational – cohort	Lièvre et al (88)	2008	10.1200/JCO.2007.12.5906
3	Case study	Joensuu et al (89)	2001	10.1056/NEJM200104053441404
4	Literature review ◆	DiMasi & Grabowski (90)	2007	10.1200/JCO.2006.09.0803
5	Literature review ◆	Von Hoff (91)	1998	n/a
6	Randomised controlled trial	Thatcher et al (92)	2005	10.1016/S0140-6736(05)67625-8
7	Randomised controlled trial	Mok et al (93)	2009	10.1056/NEJMoa0810699
8	Observational – cohort	Von Hoff et al(94)	2010	10.1200/JCO.2009.26.5983

9	Editorial	Doroshow (95) [comment on Von Hoff 2010]	2010	10.1200/JCO.2010.31.1472
10	Randomised controlled trial	Kim et al (96)	2011	10.1158/2159-8274.CD-10-0010

Table 5 - evidence cited for biomarker inclusion by the SHIVA randomised controlled trial. Based on 2014 protocol for SHIVA (41).

Table 6: Full list of evidence cited by GIST trial in biomarker review

No.	Type of reference	Author(s)	Year	DOI
1	Epidemiology – American Heart Association	Mozaffarian et al(97)	2015	10.1161/CIR.0000000000000157
2	Editorial	Greenland and Lauer(98)	2015	10.1001/jama.2015.7434
3	Meta-analysis (of IPD)	Cholesterol Treatment Triallists' Collaborators(99)	2012	10.1016/S0140-6736(12)60367-5
4	Meta-analysis (of IPD)	Cholesterol Treatment Triallists' Collaborators(100)	2015	10.1016/S0140-6736(14)61368-4
5	Cochrane review	Taylor et al(101)	2013	10.1002/14651858.CD004816.pub5
6	Guidelines - American College of Cardiology/American Heart Association Task Force	Stone et al(102)	2013	10.1016/j.jacc.2013.11.002
7	Observational – cohort	Pencina et al(103)	2014	10.1056/NEJMoa1315665
8	Literature review	Hirsh et al(104)	2015	10.1016/j.jacc.2015.05.030
9	Observational – cohort	Bermingham et al(105)	2011	10.1016/j.clinthera.2011.07.007
10	Observational – cohort	Ho et al(106)	2008	10.1016/j.ahj.2007.12.011
11	Observational – cohort	Vodonos et al(107)	2015	10.1016/j.ejim.2015.02.014
12	Observational – cohort	Franklin et al(108)	2015	10.1002/pds.3787
13	Systematic review	De Vera et al(109)	2014	10.1111/bcp.12339
14	Literature review	Osterburg and Blaschke(110)	2005	10.1056/NEJMra050100
15	Qualitative study	Fung et al(111)	2010	n/a
16	Qualitative study	Cohen et al(112)	2012	10.1016/j.jacl.2012.03.003
17	Literature review	Ong et al(113)	2012	10.2217/pgs.12.2
18	Guidelines – American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute	Pasternak et al(114)	2002	10.1016/S0735-1097(02)02030-2
19	Expert opinion	Thompson et al(115)	2006	10.1016/j.amjcard.2005.12.013
20	Literature review/expert opinion	Alfirevic et al(116)	2014	10.1038/clpt.2014.121

21	Literature review	Patel et al(117)	2015	10.1016/j.atherosclerosis.2015.03.025
22	Guidelines – European Atherosclerosis Society	Stroes et al(118)	2015	10.1093/eurheartj/ehv043
23	Observational – case control	Link et al(119)	2008	10.1056/NEJMoa0801936
24	Meta-analysis	Hou et al(120)	2015	10.1097/MD.0000000000001268
25	Observational – cohort	Pasanen et al(121)	2006	10.1007/s00228-006-0123-1
26	In vitro work	Kimoto et al(122)	2012	10.1021/mp300379q
27	Randomised controlled trial	Voora et al(123)	2009	10.1016/j.jacc.2009.04.053
28	Guidelines – Clinical Pharmacogenetics Implementation Consortium	Wilke et al(124)	2012	10.1038/clpt.2012.57
29	Observational – cohort	Birmingham et al(125)	2015	10.1007/s00228-014-1801-z
30	Observational – cohort/meta-analysis	de Keyser et al(126)	2014	10.1097/FPC.0000000000000018
31	Sub-study of larger randomised controlled trial	Danik et al(127)	2013	10.1016/j.ahj.2013.01.025
32	Sub-study of larger randomised controlled trial	Martin et al(128)	2011	10.1111/j.1365-2125.2011.04090.x
33	Literature review	Niemi et al(129)	2011	10.1124/pr.110.002857
34	Guidelines – Clinical Pharmacogenetics Implementation Consortium	Ramsey et al(130)	2014	10.1038/clpt.2014.125
35	Literature review	Voora and Ginsburg(131)	2012	10.1016/j.jacc.2012.01.067
36	Observational – cohort	Donnelly et al(132)	2011	10.1038/clpt.2010.255
37	Observational – cohort (pilot study)	Li et al(133)	2014	10.3390/jpm4020147

Table 6 - evidence cited for biomarker inclusion by the GIST randomised controlled trial. Based on 2016 protocol for GIST (42).

Table 7: Full list of evidence cited by Precision Medicine Guided Treatment for Cancer Pain trial in biomarker review

No.	Type of reference	Author(s)	Year	DOI
1	Guidelines – National Cancer Institute	PDQ Supportive and Palliative Care Editorial Board (134)	2002	n/a
2	Guidelines – National Comprehensive Cancer Network	National Comprehensive Cancer Network (135)	2017	n/a
3	Randomised controlled trial	Temel et al (136)	2010	10.1056/NEJMoa1000678
4	Guidelines – European Association for Palliative Care	Caraceni et al (137)	2012	10.1016/S1470-2045(12)70040-2
5	Expert panel	Fine et al (138)	2009	10.1016/j.jpainsymman.2009.06.002
6	Observational – cohort	Zhao et al (139)	2014	10.1200/JCO.2013.50.6071

7	Randomised controlled trial (in twins)	Angst et al (140)	2012	10.1016/j.pain.2012.02.022
8	Literature review	Fillingim et al (141)	2008	10.1111/j.1601-0825.2008.01458.x
9	Observational – cohort	Gan et al (142)	2007	10.1007/BF03256239
10	Case study	Susce et al (143)	2006	10.1016/j.pnpbp.2006.03.018
11	Guidelines – Clinical Pharmacogenetics Implementation Consortium	Crews et al (144)	2014	10.1038/clpt.2013.254
12	Observational – cohort	Baber et al (145)	2015	10.1038/tpj.2015.3
13	Case study	Ciszkowski et al (146)	2009	10.1056/NEJMc0904266
14	Case study	Gasche et al (147)	2004	10.1056/NEJMoa041888
15	Randomised controlled trial	Eckhardt et al (148)	1998	10.1016/S0304-3959(98)00021-9
16	Randomised controlled trial	Lötsch et al (149)	2009	10.1016/j.pain.2009.03.023
17	Observational – cohort	Andreassen et al (150)	2012	10.1007/s00228-011-1093-5
18	Randomised controlled trial	Samer et al (151)	2010	10.1111/j.1476-5381.2010.00673.x
19	Randomised controlled trial	Zwisler et al (152)	2009	10.1111/j.1742-7843.2009.00378.x
20	Observational – cohort	Zwisler et al (153)	2010	10.1111/j.1399-6576.2009.02104.x

Table 7 - evidence cited for biomarker inclusion by the Precision Medicine Guided Treatment for Cancer Pain trial. Based on 2018 publication (43).

Chapter 4

4.1 Protocol for systematic reviews and meta-analyses

See: citation (154)

Danielle Johnson, Andrea Jorgensen. The influence of HLA-B*15:02 and HLA-A*31:01 on the risk of developing adverse skin reactions to carbamazepine: protocol for two systematic reviews. PROSPERO 2019 CRD42019161000 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019161000

4.2 Standard data extraction form for systematic reviews

DATA EXTRACTION FORM: SYSTEMATIC REVIEW OF PGx STUDIES OF HLA-B*15:02 AND CARBAMAZEPINE-INDUCED HYPERSENSITIVITY REACTIONS

REVIEWER: DJ ALJ

PDF ID:	**Lead Author:**	**Publication Date:**

1. General Notes of Interest

Input any general comments of interest here

****

2. Study Design

a) Design: RCT prospective cohort retrospective cohort case-control

case-control + healthy subjects other(describe)…….

b) Sample size (if case-control study state numbers separately): **total** cases controls
☐ healthy

c) Is justification/calculation given for sample size ? yes no

d) Is a priori power to detect effect sizes of varying degrees quoted ? yes no

****

3. Participants

a) Ethnic groups included: White Black African Black Caribbean Black other
Indian Bangladeshi Pakistani Chinese Japanese
African American Other(describe)……..

b) What is inclusion/exclusion criteria ? Describe.

Inclusion
Cases:
Controls:
Exclusion

c) What reactions were included? SJS TEN SJS/TEN DRESS MPE other

(describe)……

d) Patient characteristics (please continue on additional sheet if not enough space)

Characteristic	**Units**	**Overall**	**Subgroup** **Cases (n=**	**Subgroup** **Controls (n=**	**Subgroup** **Healthy volunteers (n=**	**Other Subgroup … (n=**
Age (mean+/- SD; range) /(median; IQR)[1]						
No. males n (%)						
Ethnicity: White n (%)						
Black African n (%)						
Black Caribbean n (%)						
Black other n (%)						

Indian n (%)						
Bangladeshi n (%)						
Pakistani n (%)						
Chinese n (%)						
Japanese n (%)						
African American n (%)						
Other……..						
Indication for carbamazepine: n (%)						
Epilepsy/seizures						
Psychiatric						
Neuralgia						
Neuropathic pain						
Autism						
Other……						
Other……						

Other……..						
Other…….						

Notes

1. **Cross out one that doesn't apply**

*****

Notes

1. **Add any relevant comments here e.g. if the row corresponds to a specific ethnic subgroup within the study)**

b) Are results given for all ? yes no(explain)……

c) Were genotyping personnel blinded to outcome/case-control status? yes not mentioned

d) i. Was test for HWE undertaken at each SNP ? yes not mentioned

ii. If yes, what test was used ? Chi-square Fisher's Exact other (describe) not stated n/a

iii. What p-value cut-off was used ?..... n/a

iv. Are results of testing provided ? yes no n/a

v. If yes, how many SNPs were found to deviate ?.....n/a

vi. If yes and more than one deviates, are reasons for deviation explored ?

yes not mentioned n/a

vii. Are deviating SNPs excluded from analyses ? yes no unclear n/a

e) i. Is method of genotyping described ? yes no

ii. If yes, describe briefly……..

f) i. Were genotype QC methods used ? yes not mentioned

ii. If yes, what method was used ? resequencing all patients resequencing random sample resequencing extreme patients regenotyping all patients regenotyping random sample regenotyping extreme patients other (describe) not stated n/a

iii. If yes, were results quoted ? yes no n/a

iv) If so what was degree of agreement ? …… n/a

g) Were genotype frequencies compared with previously published for same population ?

yes not mentioned

*****

b) i. Is extent of missing data stated ? yes no

ii. If yes, are reasons for missingness explored ? yes no none are missing n/a

iii. Are any checks undertaken for missingness at random ? yes not mentioned

iv. Is missing genotype data imputed ? yes no unclear

v. If so, how ? multiple imputation other (describe)…….. n/a

vi. Are numbers contributing to each analysis quoted ? yes no

vii. If so, are numbers different to total sample size ? yes no n/a

6. Outcomes

a) Was justification given for choice of outcomes ? yes(describe below) no

Justification for choice of outcomes

b) List any particular outcome(s) that appear(s) to be suppressed (describe)……..

****

7, Results

Outcome	Outcome	HLA-B*15:02 present	HLA-B*15:02 not present	p-value vs outcome present	Definition	Test undertaken	Additional Comments*
ADR overall	Present						
	Absent; controls						
	Absent; HV						
SJS	Present						
	Absent; controls						
	Absent; HV						
TEN	Present						
	Absent; controls						

	Absent; HV						
SJS/TEN	**Present**						
	Absent; controls						
	Absent; HV						
DRESS	**Present**						
	Absent; controls						
	Absent; HV						
MPE	**Present**						
	Absent; controls						
	Absent; HV						
Other (describe)	**Present**						
	Absent; controls						
	Absent; HV						
Other (describe)	**Present**						
	Absent; controls						
	Absent; HV						

* e.g. particular ethnicities only, and whether the absent includes CBZ-tolerant patients or healthy patients. HV = healthy volunteers

4.3 Full list of studies included in systematic reviews and meta-analyses

See https://www.dropbox.com/scl/fi/fozqjovdao5qr1da2wwhg/allpapers_table.xlsx?dl=0&rlkey=nop19t2e0sukgme5ice8f0q88

4.4 Quality assessment of studies included in systematic reviews and meta-analyses

4.4.1 HLA-B*15:02

See https://www.dropbox.com/scl/fi/5pvj5sp03gehx8kejet1y/Study-quality-1502.xlsx?dl=0&rlkey=dugxpbi1nvvqaqbolv83iwljw

4.4.2 HLA-A*31:01

See https://www.dropbox.com/scl/fi/r7c6qqvhr3a8vir9hvkh2/Study-quality-3101.xlsx?dl=0&rlkey=w4f5a6qz9dcahaxdcm7gke1gg

4.5 Calculation of allele frequencies for *HLA-B*15:02* and *HLA-A*31:01*

See https://www.dropbox.com/scl/fi/0avm3a85rj3gg7x49eyti/allele_freq_1502_3101_20211109.xlsx?dl=0&rlkey=aa96zen4gbywrfyc89pgn9vnq

4.6 Simulation code

See https://github.com/dkj201/simulation for full details.

Table 8: Comparison of papers included in previous meta-analyses and our meta-analysis.

Previous meta-analysis	Included paper [by ancestry subgroup]	Included in current MA?	Reasons
Yip et al 2012 (155)	Hung et al 2006 [Han Chinese]	Y	NA
	Wu et al 2010 [Han Chinese]	Y	NA
	Liao et al 2010 [Han Chinese]	N	Previously excluded as is meeting abstract only
	Zhang et al 2011 [Han Chinese]	Y	NA

	Wang et al 2011 [Han Chinese]	Y	NA
	Locharernkul et al 2008 [Thai]	N	SJS and TEN reported separately.
	Tassaneeyakul et al 2010 [Thai]	Y	NA
	Kulkantrakorn et al 2012 [Thai]	N	Data is included within Tassaneeyakul 2010
	Then et al 2011 [Malaysian]	N	SJS only, not SJS/TEN
Tangamornsuksan et al 2013 (156)	Alfirevic et al 2006 [White] *	N	No HLA-B*15:02 positive patients
	Hung et al 2006 [Han Chinese]	Y	NA
	Liao et al 2010 [Han Chinese]	N	Previously excluded as is meeting abstract only
	Wu et al 2010 [Han Chinese]	Y	NA
	Zhang et al 2011 [Han Chinese]	Y	NA
	Shi et al 2012 [Han Chinese]	Y	NA
	Locharernkul et al 2008 [Thai]	N	SJS and TEN reported separately
	Tassaneeyakul et al 2010 [Thai]	Y	NA
	Kim et al 2011 [Korean]	N	SJS only, not SJS/TEN
	Then et al 2011 [Malaysian]	N	SJS only, not SJS/TEN
	Niihara et al 2012 [Japanese] *	N	No HLA-B*15:02 positive patients
Grover et al 2014 (157)	Cheung et al 2013 [Han Chinese]	Y	NA
	Hung et al 2006 [Han Chinese]	Y	NA
	Shi et al 2012 [Han Chinese]	Y	NA
	Wang et al 2011 [Han Chinese]	Y	NA
	Wu et al 2010 [Han Chinese]	Y	NA
	Zhang et al 2011 [Han Chinese]	Y	NA

	Kim et al 2011 [Korean]	N	SJS only, not SJS/TEN
	Then et al 2011 [Malaysian]	N	SJS only, not SJS/TEN
	Kulkantrakorn et al 2012 [Thai]	N	Data is included within Tassaneeyakul 2010
	Locharernkul et al 2008 [Thai]	N	SJS and TEN reported separately.
	Tassaneeyakul et al 2010 [Thai]	Y	NA

Table 8 - Comparison of papers included in previous meta-analyses and our meta-analysis.

Chapter 5

Table 9: Previous systematic reviews of discrete choice experiments

Reference	Summary	Aim	No. of included DCEs	Date range included	Populations	Key findings
Ryan and Gerard (2003) (158)	Systematic review of DCEs in health economics	To identify current practice in DCEs in health economics. Also evaluated study quality	34	1990- 2000	Patients Community Health insurance consumer	No studies judged to be of 'strong' design quality
de Bekker-Grob, *et al.* (2010) (159)	Updated systematic review of DCEs in health economics	To update the previous review (158) with current practice in DCEs in health economics	114	2001- 2008	Not reported	Large increase in use of DCEs in health economics, with changing methodologies
Clark, *et al.* (2014) (160)	A further updated systematic review of DCEs in health economics	To update the previous review (159) with current practice in DCEs in health economics	179	2009- 2012	Not reported	Further increase in use of DCEs, particularly in countries other than the UK

Soekhai, *et al.* (2019) (161)	A large systematic review of health-related DCEs	To provide an overview of DCEs in health economics, and their applications and methods	301	2013 - 2017	Patients Healthcare workers General public	Reflects on more modern DCE methods and design, but problems with poor reporting continue
Guerra, *et al.* (2019) (162)	A small systematic review of patient preferences for breast cancer treatment	To qualitatively synthesis information from DCEs about breast cancer treatment in patients	5	- (May) 2019	Patients	Patients most highly value attributes related to side-effects
Trapero-Bertran, *et al.* (2019) (163)	A systematic review of DCEs relating to priority setting in health care provision	To identify attributes for designing a DCE, to develop and validate a framework for decision making on health technologies	72	2008 - 2015	Patients Policy makers Providers General public	Better quality DCEs in heath care provision are needed, especially in areas other than oncology
Bien, *et al.* (2017) (164)	A systematic review of patient preferences for cancer treatment	To focus on DCEs in cancer treatment and assess the significance of different attribute types	28	2010- (April) 2016	Patients General population Healthcare professionals	Attributes related to side-effects were most often significant
Harrison, *et al.* (2017) (165)	Systematic review of DCEs comparing patients' and healthcare professionals' views	Review DCEs that that elicited opinions from both patients and healthcare professionals and examine concordance	38	1995- (July) 2015	Patients General public Parents/caregivers Healthcare professionals	Patients and healthcare professionals value attributes differently and more DCEs should incorporate this analysis
Vass, *et al.* (2017) (166)	Systematic review of qualitative methods in DCE practice	Explore the use of qualitative methods in healthcare related DCEs and explore their perceived usefulness with authors	254	2001- (June) 2012	Not reported	Only a minority of DCEs used 'extensive' qualitative work, although authors agree on its usefulness
Harrison, *et al.* (2014) (167)	Systematic review of DCEs that included a risk attribute	To highlight the use of risk in DCEs, and recommend ways to improve risk communication	117	1995- (April) 2013	Patients Healthcare professionals Public Parents Decision makers	Recommendation that risks should be placed in context and methods used to communicate risk should be validated

Table 9 - A summary of previous systematic reviews of discrete choice experiments. The highlighted rows show 4 linked reviews, each using the same methods to update on the field of health related DCEs. DCEs = discrete choice experiments

Table 10: Search terms used by previous systemic reviews to locate discrete choice experiments

	Ryan & Gerard (2003) (158)	de Bekker-Grob, *et al.* (2010) (159)	Clark, *et al.* (2014) (160)	Soekhai, *et al.* (2019) (161)	Guerra, *et al.* (2019) (162)	Trapero-Bertran, *et al.* (2019) (163)	Bien, *et al.* (2017) (168)	Harrison, *et al.* (2017) (165)	Vass, *et al.* (2017) (166)	Harrison, *et al.* (2014) (167)
Choice behaviour					✓					✓
Choice Behaviour (MeSH term)					✓					
Choice experiment					✓					
Choice model					✓					
Conjoint	✓		✓				✓			
Conjoint analysis	✓	✓	✓	✓	✓	✓	✓		✓	
Conjoint-analysis					✓					
Conjoint analysis/ measurement/ study/ choice								✓		✓
Conjoint choice experiment			✓	✓			✓			
Conjoint choice experiment(s)		✓				✓			✓	
Conjoint choice experiments	✓			✓						
Conjoint measurement	✓	✓	✓	✓		✓	✓		✓	

Conjoint studies	✓	✓	✓	✓		✓	✓		✓	
DCE			✓							
Discrete choice					✓			✓		✓
Discrete-choice					✓					
Discrete choice conjoint experiment			✓	✓			✓			
Discrete choice conjoint experiments				✓						
Discrete choice experiment			✓	✓			✓			
Discrete choice experiment(s)		✓				✓			✓	
Discrete choice experiments										
Discrete choice model(l)ing		✓	✓			✓	✓		✓	
Discrete choice modeling				✓						
Discrete choice modelling	✓			✓						

Discrete-choice										
Functional measurement	✓	✓	✓	✓		✓			✓	
Paired comparison					✓			✓		✓
Paired comparisons	✓	✓	✓	✓		✓			✓	
Pairwise choice					✓			✓		✓
Pairwise choices	✓	✓	✓	✓		✓			✓	
Part-worth utilities	✓	✓	✓	✓		✓			✓	
Part-worth utility								✓		✓
Patient preference					✓		✓			
Patient Preference (MeSH term)					✓					
Preference					✓					
Stated preference	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 10 - Grid showing search terms used by previous systematic reviews to locate discrete choice experiments.

Table 11: Data extraction sheet prepared for systematic review of discrete choice experiments

Title	
Authors	
DOI	
Link	

Year of publication	
Country of origin	
Pharmacogenetic phenotype	
Disease	
Biomarker(s)	
Sample size	
Population type	
Population age	
Population race or ethnicity	
Population gender (% female)	
Response rate	
Number of choice tasks seen by each participant	
Number of possible choice tasks	
Survey method	
Number of attributes	
Attribute domains	
Design plan	
Design software	
Method(s) used to create choice sets	
Estimation procedures	

Validity checks	
Qualitative work	
Learning from this DCE	

Table c11 - Standard data extraction prepared for systematic review of discrete choice experiments. DCE = discrete choice experiment. DOI = digital object identifier.

Table 12: Data extracted from each paper in the systematic review of discrete choice experiments (1)

First author / reference	Year	Country	PGx	Disease	Biomarker(s)	Sample size	Pop.	Age	Race/ ethnicity	Gender %F	Response rate	Learning
Ballinger (169)	2017	USA	Risk of ADRs (peripheral neuropathy and congestive heart failure)	Breast cancer	HER2 (negative only)	417	Patients	35% under 50 65% 50 or over	88% Caucasian 5% African American 4% Hispanic 3% Other	Not reported	Not reported	Previous experience of an ADR affects preferences
Boeri (170)	2018	UK	Risk of ADRs (10kg weight gain), hyper-responsiveness genotype	Schizophrenia	n/a	67	HCPs	Not reported	Not reported	41%	95.7%	HCPs are open to PGx but this varies depending on experience
Chan (171)	2013	Singapore	Risk of ADRs (major bleeding or clotting), genetic vs non-genetic test	CV disease	CYP2C9 VKORC1	197	General public	Mean: 52.5	100% Chinese	72.7%	83.5%	Presentation of warfarin and ADRs to general public
							Patients	Mean 57.4	100% Chinese	26.9%	53.8%	

Dong (172)	2016	Singapore	Risk of ADRs (SJS), cost of genetic test, change in cost of medications depending on genetic test result	Gout	HLA-B*58:01	189	Patients	Mean 57.1	61% Chinese 27% Indian 10% Malay 2% Other	34%	Not reported	Uptake as a useful output of a DCE
Herbild (173)	2009	Denmark	Time spent with dosage adjustments due to lack of effect or ADRs (not specified), likelihood of improvements from genetic test	Depression	CYP2D6	323	General public	Not reported	Not reported	53%	46%	Participants that don't normally pay for healthcare can consider cost in decision making
Issa (174)	2013	USA	If test predicts risk of recurrence, likelihood of benefit from drugs, and risk of ADRs (not specified)	Breast cancer	Oncotype DX	150	Patients	Mean 54.5	81% White 10% African-American 6% Hispanic/Latino 3% Asian/Asian American	Breast 100%	42.2%	Detailed report of focus group methodology for attribute and level selection
				Colorectal cancer	KRAS UGT1A1	150	Patients	Mean 42 (colorectal)	74% White 10% African-American 9% Hispanic/Latino 3% Asian/Asian American 3% American-Indian/Alaska Native 1% Hawaiian Native/Pacific Islander	Colorectal 46%		
Liede (175)	2017	Int	Risk of ADR (teeth and jaw problems, uterine cancer), type of ADR (effect on fertility, effect on female hormones)	Breast cancer	BRCA1 BRCA2	622	Patients*	Mean 41	Not reported	100%	53.5%	External validity checks are useful, where possible
Marshall (176)	2016	Canada	Risk of ADR [categorical] (temporary side-effects, permanent side-effects), likelihood of	Breast cancer	HER2	1004	General public	Mean 49	84% White 6% Chinese 2% Indigenous 1% Black 5% Other 2% Not answered	100%	Not reported	High levels of evidence assured if a test is insurance covered

			benefit from chemotherapy									
Marshall (177)	2017	USA	Risk of ADR (that makes you unable to do everyday activities or take care of yourself)	None	Whole genome sequencing	410	General public	Not reported	Not reported	Not reported	47.0%	Pictograms to represent risks
Najafzadeh (178)	2013	Canada	Risk of ADR (nausea, hair loss, skin rash, fatigue), severity of ADR (mild, moderate, severe)	Cancer	None – hypothetical test	1096	General public group A ‡	Mean 48.2	Not reported	48.5%	65%	Participants can tolerate complex information
							General public group B	Mean 47.6	Not reported	50.6%	69%	
							Patients	Mean 58.2	Not reported	58.3%	64%	
Payne (179)	2011	UK	Risk of ADR (azathioprine-associated neutropenia)	Autoimmune disease	TPMT	297	Patients	Mean 45.8	Not reported	56%	50%	Ethical considerations of including a cost attribute
							HCPs	Not reported	Not reported	Not reported	34%	
Powell (180)	2015	UK	Risk of ADR (mild skin rash, memory problems, SJS), likelihood of benefit	Epilepsy	HLA-A*31:01	165	HCPs	Not reported	Not reported	Not reported	Not reported	Utility model for predicting uptake based on results of DCE
							Patients	Median 38	90.2% White 3.7% Black 1.2% Asian 2.4% Mixed/multiple	66%	Not reported	

Smith (181)	2014	USA	Risk of ADR (peripheral neuropathy, severe diarrhoea), type of ADR (moderate or severe), duration of ADR (1 year, just during treatment)	Breast cancer	None – hypothetical test	641	Patients	Most respondents 50-59	90.6% Caucasian No other reported	99.7%	Not reported	Participants are able to comprehend and manage decisions based on genetic biomarkers

*Table 12 - Data extracted from each paper in DCE systematic review. Does not include some fields extracted – DOI, title, full author list. * Women with BRCA1 or BRCA2 mutations but unaffected by breast or ovarian cancer. ‡ The general public was split into 2 groups and each was presented with a unique scenario. Results were reported separately ADRs = adverse drug reactions. CV = cardiovascular. HCPs = healthcare professionals. PGx = pharmacogenetics. Pop. = population. SJS = Stevens Johnson syndrome.*

Table 13: Data extracted from each paper in the systematic review of discrete choice experiments (2)

First author	Year	No. of choice tasks	No. of possible choice tasks	Survey method	No. of attributes	Attribute domains	Design plan	Design software	Method(s) used to create choice sets	Estimation procedures	Validity checks	Qualitative work
Ballinger (169)	2017	12	Not reported	Online	4	Health status Risk	Not reported	Not reported	Pragmatically chosen	Hierarchical Bayesian	Theoretic	Not reported
Boeri (170)	2018	26	26	Face to face	4	Health status Risk Time Other	Fractional factorial	NGene	D-efficiency	Random parameters logit	Not reported	Expert opinion
Chan (171)	2013	8	24	In clinic Online	4	Health care Money Risk Other	Not reported	Sawtooth CBC/Web	Not reported	Hierarchical Bayesian	Sen's expansion/ contraction	Pilot testing
Dong (172)	2016	9	32	Face to face	5	Money Risk Other	Main and interaction effects	SAS	D-efficiency	Latent class logit	Non-satiation Transitivity	Patient interviews Cognitive interviews
Herbild (173)	2009	8	32	Online	4	Health care Money Risk Time	Fractional factorial	SAS	D-efficiency	Conditional logistic regression	Theoretic	Expert opinion Focus groups [published]

Issa (174)	2013	20	Not reported	Online	5	Health care Health status Money Risk Other	Not reported	Sawtooth (custom)	Random pairing	Not reported	Sen's expansion/ contraction	Focus groups [published]
Liede (175)	2017	4	36	Online	7	Health status Risk Time Other	Fractional factorial	SAS	D-efficiency	Random parameters logit	External	Expert opinion Patient interviews
Marshall (176)	2016	12	500	Online	5	Health care Risk Other	Main and interaction effects	Sawtooth CBC/Web	D-efficiency	Hierarchical Bayesian	Sen's expansion/ contraction Theoretic	Expert opinion Focus groups Pilot testing [published]
Marshall (177)	2017	6	Not reported	Online	3	Health care Money Risk	Main effects	SAS	Not reported	Random parameters logit	Theoretic	Expert opinion Interviews
Najafzadeh (178)	2013	16	160	Online	7	Health status Money Risk Time Other	Fractional factorial	Sawtooth CBC/Web	D-efficiency	Conditional logit	Non-satiation Theoretic	Expert opinion Pilot testing
Payne (179)	2011	16	16	Post	5	Risk Time Other	Fractional factorial	Not reported	Unclear (Street and Burgess methods)	Random effects probit	Non-satiation Sen's expansion/ contraction Theoretic	Expert opinion Focus groups Interviews Pilot testing [published]
Powell (180)	2015	16 (HCPs) 8 (patients)	Not reported	Online	6 (HCPs) 5 (patients)	Money Risk Time Other	Fractional factorial	Not reported	Pairing with constant comparator (HCPs) Not reported (patients)	Random effects logit	Not reported (HCPs) Non-satiation (patients)	Interviews Focus groups
Smith (181)	2014	14	Not reported	Online	4	Health care Health status Risk	Not reported	Not reported	Not reported	Not reported	Sen's expansion/ contraction	Pilot testing

Table 13 - Further data extracted for each paper in DCE systematic review.

Chapter 6

6.1 Survey of healthcare professionals

Questionnaire for healthcare professionals

Welcome

Thank you for participating in our survey. Your feedback is important for designing a questionnaire that will be useful to patients, academics, and anyone with an interest in pharmacogenetics.

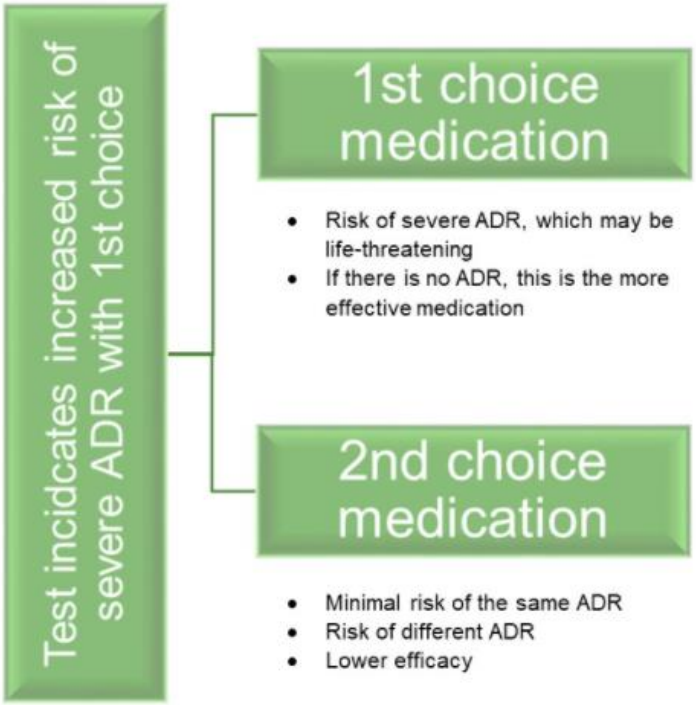
This survey has been approved by the University of Liverpool Health and Life Sciences Research Ethics Committee (ref. 4736).

Background information

Genetic testing can be used to predict and prevent adverse drug reactions (ADRs). This is termed pharmacogenetics and is one of the promises of personalised medicine. The FDA defines pharmacogenetics as 'variations in DNA sequence as related to drug response'.

Although there are some examples of this in use in the clinic (see below), pharmacogenetics is still a comparatively new field with many unknowns. We are therefore designing a survey to quantify the general public's views on genetic testing to prevent ADRs.

The scenario we will test is one where a patient has a genetic test indicating they are at increased risk of an ADR with a first-choice medication. We want to interrogate in which scenarios participants would choose a second-choice, potentially less effective medication, and when they would choose to risk the ADR with the first-choice medication.



You have been invited to take this survey since you are a professional interested in personalised medicine. The results of this survey will be used alongside opinions from patients and the general public, to design a national survey.

Next

Examples

Abacavir, hypersensitivity syndrome in HIV, and HLA-B*57:01

Abacavir is an antiretroviral drug for HIV treatment. A hypersensitivity syndrome initially presenting as fever, rash, nausea and vomiting, potentially leading to severe hypotension and death is strongly associated with the HLA-B*57:01 allele, and can be avoided by withholding abacavir from patients testing positive for HLA-B*57:01.

The British National Formulary, European Medicines Agency and British HIV Association recommend testing every patient before commencing abacavir.

Carbamazepine, Stevens-Johnson syndrome in epilepsy and HLA-B*15:02

Carbamazepine is a tricyclic anticonvulsant used to treat epileptic seizures, trigeminal neuralgia, and some psychiatric disorders. It is linked to the rare but extremely serious Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) reactions.

HLA-B*15:02 is strongly associated with SJS/TEN in patients receiving carbamazepine. The British National Formulary specifies that individuals of Han Chinese or Thai origin are tested for the HLA-B*15:02 allele, and to avoid carbamazepine unless there is no alternative.

Survey

Below is a list of characteristics that might be considered important when deciding whether to order a pharmacogenetic test. Please select the top characteristic in each group that you think is the most important in making the decision to order a genetic test. Please then write a little to explain your choice.

* **Test characteristics**

- ◯ Time to result
- ◯ Cost of test
- ◯ Level of evidence for testing (e.g. one or more randomised controlled trials, compared to a test with only a genome-wide association study [GWAS] behind it)
- ◯ Coverage of the test (test can predict either severe ADRs only, or severe and mild ADRs)
- ◯ PPV (probability of experiencing the ADR if a positive result on the pharmacogenetic test – 'true positive')
- ◯ NPV (probability of not experiencing the ADR if a negative result on the pharmacogenetic test – 'true negative')
- ◯ If the test included in BNF
- ◯ Other (please specify)

Reason(s) for selection:

* **Medication choices**

- ◯ Efficacy/effectiveness of first- and second-choice medications
- ◯ Risk of severe ADRs with first- and second-choice medications
- ◯ Risk of mild ADRs with first- and second-choice medications
- ◯ Cost/cost-effectiveness of first- and second-choice medications
- ◯ Other (please specify)

Reason(s) for selection:

* **Test information**

- ◯ Information on specific gene polymorphism(s)
- ◯ A panel of several pharmacogenes that may yield useful results to inform future prescribing decisions
- ◯ Whole genome sequencing
- ◯ What does the test result mean (easily understandable interpretation of the test result)
- ◯ Other (please specify)

Reason(s) for selection:

* **Practicalities**

- ◯ How sample is collected (saliva, blood, etc)
- ◯ Who is involved in ordering, interpreting and explaining results to patients
- ◯ Privacy of test results (restricted to doctor-patient, use for research, use by insurance companies)
- ◯ Other (please specify)

Reason(s) for selection:

Please add any further characteristics you think are important. There are no wrong answers here, please write down anything that comes to mind as this will help us in designing the survey.

Please could you write a little to help us understand the reasons for your choices. [Optional]

Prev Next

Survey

Below is a list of characteristics that might be considered important when deciding whether to order a pharmacogenetic test. Please select the top characteristic in each group that you think is the most important in making the decision to order a genetic test. Please then write a little to explain your choice.

* **Test characteristics**

- ◯ Time to result
- ◯ Cost of test
- ◯ Level of evidence for testing (e.g. one or more randomised controlled trials, compared to a test with only a genome-wide association study [GWAS] behind it)
- ◯ Coverage of the test (test can predict either severe ADRs only, or severe and mild ADRs)
- ◯ PPV (probability of experiencing the ADR if a positive result on the pharmacogenetic test – 'true positive')
- ◯ NPV (probability of not experiencing the ADR if a negative result on the pharmacogenetic test – 'true negative')
- ◯ If the test included in BNF
- ◯ Other (please specify)

Reason(s) for selection:

* **Medication choices**

- ◯ Efficacy/effectiveness of first- and second-choice medications
- ◯ Risk of severe ADRs with first- and second-choice medications
- ◯ Risk of mild ADRs with first- and second-choice medications
- ◯ Cost/cost-effectiveness of first- and second-choice medications
- ◯ Other (please specify)

Reason(s) for selection:

* **Test information**

- ◯ Information on specific gene polymorphism(s)
- ◯ A panel of several pharmacogenes that may yield useful results to inform future prescribing decisions
- ◯ Whole genome sequencing
- ◯ What does the test result mean (easily understandable interpretation of the test result)
- ◯ Other (please specify)

Reason(s) for selection:

* **Practicalities**

- ◯ How sample is collected (saliva, blood, etc)
- ◯ Who is involved in ordering, interpreting and explaining results to patients
- ◯ Privacy of test results (restricted to doctor-patient, use for research, use by insurance companies)
- ◯ Other (please specify)

Reason(s) for selection:

Please add any further characteristics you think are important. There are no wrong answers here, please write down anything that comes to mind as this will help us in designing the survey.

Please could you write a little to help us understand the reasons for your choices. [Optional]

Prev Next

Other Information

* Your group (tick all that apply)

- [ ] GP
- [ ] Hospital doctor
- [ ] Other healthcare professional
- [ ] Academic
- [ ] Other (please specify)

If hospital doctor, what is your speciality?

If other healthcare professional, what is your speciality?

* Have you ever ordered a genetic test for a pharmacogenetic purpose?

Pharmacogenetic referring to 'variations in DNA sequence as related to drug response'.

Examples might include -

- Abacavir, hypersensitivity syndrome in HIV, and HLA-B*57:01
- Carbamazepine, Stevens-Johnson syndrome in epilepsy and HLA-B*15:02

- ◯ Yes
- ◯ No
- ◯ Unsure

* Have you ever used the results of genetic testing (ordered by yourself, other medical staff, or direct-to-consumer testing) to inform prescribing or treatment of a patient?

- ◯ Yes
- ◯ No
- ◯ Unsure

Prev Done

6.2 Survey of patients

Introduction to this survey

Genetic testing can be used to predict the risk of side-effects of some medicines.

For example, some medicines come with a risk of a painful and potentially serious skin rash as a side-effect. In the example below, if **100 people** with an illness take **medicine A**, **90 will be cured**. However, **10 of them** will suffer the potentially serious skin rash as a side-effect.

Medicine B is less effective (**only 50 out of 100 people will be cured**), but has **no risk** of this side-effect.

If 100 people take…

Medicine A

90 Will be cured

10 Will suffer a painful skin rash

Medicine B

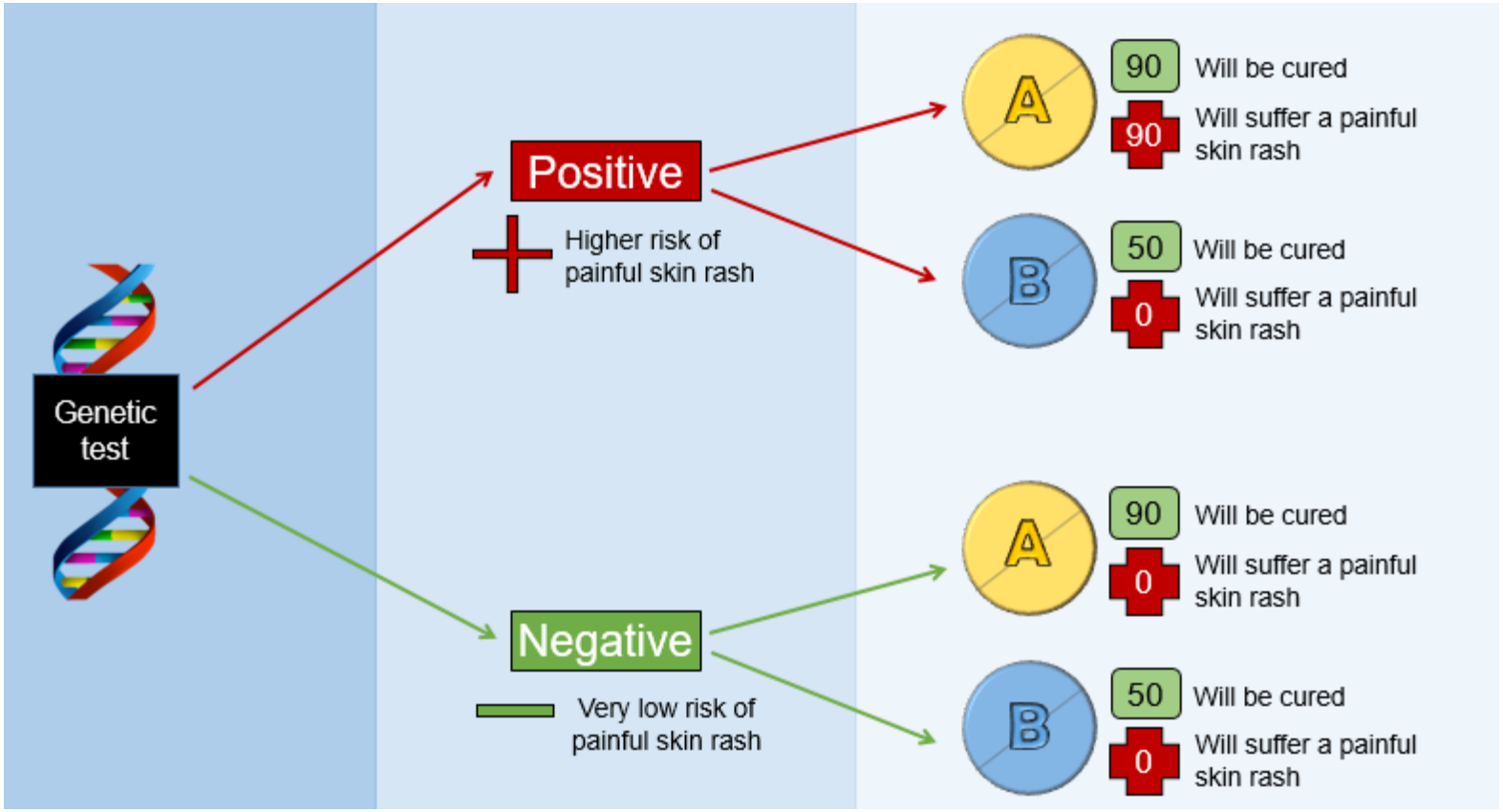
50 Will be cured

0 Will suffer a painful skin rash

You might already know which medicine you would choose if you were in this position.

However, by using genetic testing, we may be able to tell which people are more likely to suffer the painful skin rash. In this case, if someone has a negative genetic test result, we can say they have a **very low risk** of the painful skin rash if they take medicine A. They might then choose to take medicine A, to have a better chance of a cure.

But if they test positive, they would be at **higher risk** of the painful skin rash if they take medicine A. They could still choose to take it, hoping for a cure. Or, they could choose medicine B instead, where there is **no risk** of skin rash - but also less chance of a cure.


Genetic test
Positive
Higher risk of painful skin rash
Negative
Very low risk of painful skin rash
A
90
Will be cured
90
Will suffer a painful skin rash
B
50
Will be cured
0
Will suffer a painful skin rash
A
90
Will be cured
0
Will suffer a painful skin rash
B
50
Will be cured
0
Will suffer a painful skin rash

However, this is still a very new field and there are lots of things we don't know.

We wish to find out people's opinions about genetic testing to predict the risk of drug side effects, and what helps people decide if they want to have a genetic test.

* 1. Firstly, to your knowledge, have you had any genetic tests?

- ◯ Yes
- ◯ No
- ◯ Don't know
- ◯ Prefer not to answer

* 2. Imagine you have an illness where you can take medicine A or medicine B. The pictures above can help with this. There is a risk of a serious side-effect with medicine A, but it is **more effective** (works better) than B. There is **no risk** of the serious side-effect with medicine B.
A genetic test can help you and your doctor predict the risk of you getting the serious side-effect with medicine A.

Below is a list of things that might be considered important about a genetic test. Please choose the **top 5 things** you think are most important.

- [ ] **Risk of developing a severe side-effect without the genetic test**
- [ ] **Risk of developing a mild side-effect without the genetic test**
- [ ] **How well medicine A works**
- [ ] **How well medicine B works**
- [ ] **Accuracy of the genetic test** (no test is 100% accurate)
- [ ] **How much evidence is there to show that the genetic test works in predicting risk of the serious side-effect** (for example, it is used regularly by doctors, or maybe it has only been used in clinical trials. You could even be one of the first to try it)
- [ ] **Time to wait for the result**
- [ ] **Level of information you receive from the test** (you could have all your genes analysed ('gene panel test'), or just the ones relevant for medicine A)
- [ ] **Who sees the test results**
- [ ] **If your doctor recommends you receive the genetic test**

- [ ] **If most other people in your situation choose to take the genetic test**
- [ ] **Who delivers the test results to you**
- [ ] **Cost of the test to you personally**
- [ ] **Cost of the test to the NHS**
- [ ] **Cost of the medicine A to the NHS**
- [ ] **Cost of the medicine B to the NHS**
- [ ] **Severity of the disease being treated by these medications**
- [ ] **How sample is collected** (blood, saliva, biopsy, etc)

3. Please add any further things you think are important. There are no wrong answers, please write down anything that comes to mind.

2 / 4 50%

Prev Next

* 4. Which of these do you think is the **most important thing** to consider when deciding whether or not to use the genetic test?

- ◯ **Severity of the disease being treated** (it could be something that affects your life but is not life-threatening, or it could be something more serious)
- ◯ **How much evidence is there to show that the genetic test works in predicting risk of the serious side-effect** (for example, it could be used regularly by doctors, or maybe it has only been used in clinical trials. You could even be one of the first to try it)
- ◯ **How accurate the genetic test is** (no test is 100% accurate)
- ◯ **Risk of getting the serious side-effect if you take medicine A**
- ◯ **How well medicine A and medicine B work**
- ◯ **Who you see for the genetic testing service** (for example, your GP, a hospital doctor, a nurse, a genetic counsellor)
- ◯ **How the test is done** (for example, a blood sample, a saliva sample, a biopsy)
- ◯ **Privacy of your test results** (for example, only you and your doctor, or use for research also, or also being shared with an employer or life insurance company)
- ◯ Something else (please specify)

5. Please could you write a little to explain your choice.

3 / 4 75%

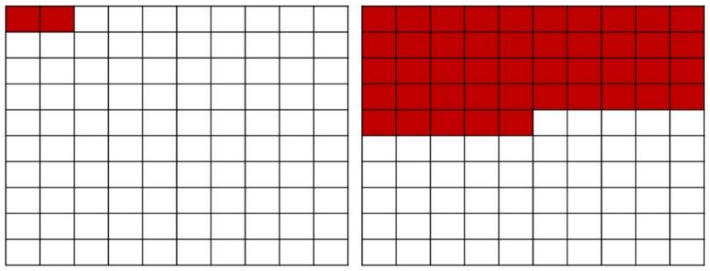
Prev Next

We would now like to ask some questions about you and how you interpret risk.

It can be difficult to clearly communicate the risk (chance) of serious side-effects. Below are four different ways it has been done in the past, using an example of two risks for comparison.

2 out of 100 people experience the serious side-effect	45 out of 100 people experience the serious side-effect

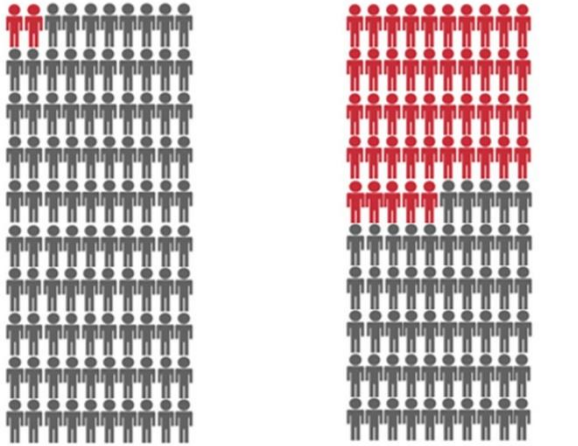
Written



2 out of 100 people experience the serious side-effect

45 out of 100 people experience the serious side-effect

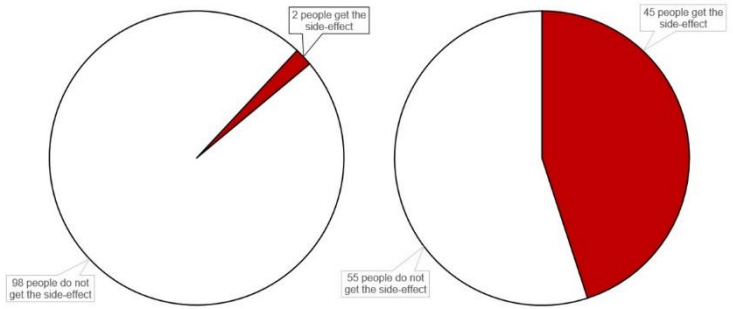
Boxes



2 out of 100 people experience the serious side-effect

45 out of 100 people experience the serious side-effect

Pictograms



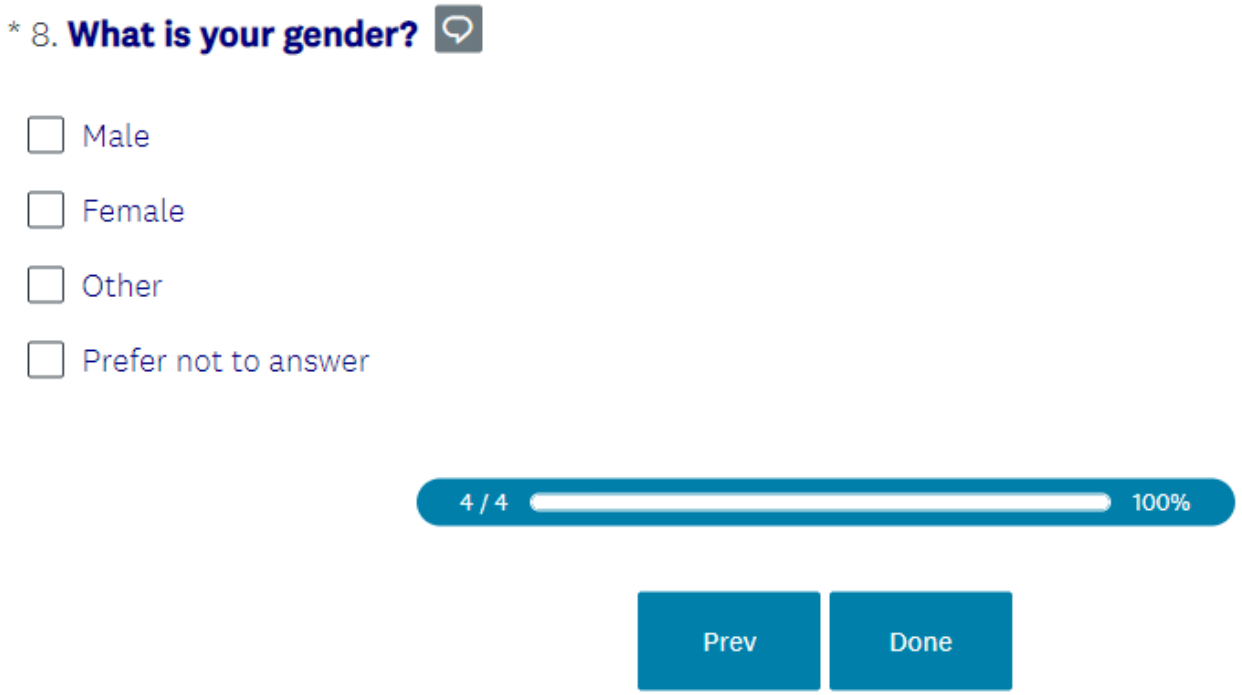
Proportion pie charts

* 6. **Which of these ways of communicating risk do you think is the clearest?**

- ◯ **Written**
- ◯ **Boxes**
- ◯ **Pictograms**
- ◯ **Proportion pie chart**
- ◯ **None of these**
- ◯ Other (please specify)

* 7. **What is your age group?**

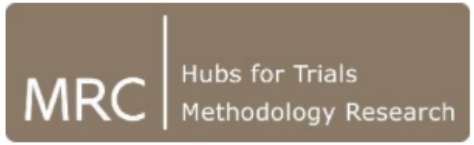
- ☐ 18-24
- ☐ 25-34
- ☐ 35-44
- ☐ 45-54
- ☐ 55 +
- ☐ Prefer not to answer



6.3 Final discrete choice experiment, as shown to participants (abacavir example)

See https://ctrc.liv.ac.uk/InDevelopment/DCE?p=test12345

Full surveys for all 8 DCEs are located here: https://www.dropbox.com/sh/yv97hf3g82pfdqv/AAD13JMDjgzvVXILUk2G20TEa?dl=0



Explanation

This is a project about the general public's opinion of using genetic testing to decide on the best treatment options for a patient. It is known as Public Opinions of PERsonalised medicine (POPPER).

The purpose of this survey is to examine whether people would choose to have a genetic test in different situations. There is some information at the start of the survey that you will need to read.

You will be asked to **imagine you have been diagnosed with a particular serious condition**, and need to be treated for it with a drug. It is known that the drug can cause side-effects in some people. You will then be asked if you would want a genetic test to help the doctor understand whether you are at risk of the side-effects, and therefore help them choose the most appropriate treatment approach for you in some different scenarios.

You might find it upsetting to imagine being diagnosed with a serious condition. You can exit the survey at any time, without giving a reason. If you have any particular concerns, you can contact one of the researchers or another organisation for support (details below)

We will not be collecting any personal information as part of this study. We will only be collecting your preferences. There are questions about your age group and gender at the end of the study, but these are **optional** and if you choose to complete them they cannot be used to identify you.

Your data will be stored on computer servers at the University of Liverpool for up to 5 years and aggregate results from the project may be published in scientific papers. The survey is being conducted through JISC, and you can view their privacy policy here.

Consent

Participation in this study is completely voluntary. If you decide not to participate there will not be any negative consequences. Please be aware that if you decide to participate, you may stop participating at any time and you may decide not to answer any specific question.

Because the data you provide is anonymous, it will not be possible to remove your data from the survey once you submit it.

By participating you are indicating that you have read the description of the study, are over the age of 18, and that you agree to the terms as described.

By clicking 'I consent' you agree to participate in this research study.

I consent | I do not consent

Details of researchers

This research is being conducted by Danielle Johnson, a postgraduate research student at the University of Liverpool. The work is supervised by Professor Andrea Jorgensen, Professor of Biostatistics, at the University of Liverpool. If you have any queries, you can contact danielle.johnson@liverpool.ac.uk or ethics@liverpool.ac.uk

This research has been approved by the University of Liverpool Health and Life Sciences Research Ethics Committee (Human participants, tissues, and databases), reference 4736. This work was funded by the MRC HTMR Network of Hubs for Trials Methodology Research (MR/L004933/2). Danielle Johnson was awarded a PhD studentship (R19) funded by the MRC HTMR Network.

Safeguarding

For mental health support: Samaritans: 116 123 (24/7) or email jo@samaritans.org

Other advice services

For advice about cancer: Macmillan Cancer Support: 0808 808 00 00 (8am-8pm, 7 days a week) or online

For advice about HIV: Terrence Higgins Trust: 0808 802 1221 (10am-6pm weekdays, 10am-1pm weekends) or info@tht.org.uk

For advice about epilepsy: Epilepsy Society: 01494 601 400 (9am-4pm Monday to Friday, 9am-7:30pm Wednesdays) or helpline@epilepsysociety.org.uk

For advice about heart disease: British Heart Foundation: 0300 330 3311 (9am-5pm weekdays, 10am-4pm Saturdays) or hearthelpline@bhf.org.uk, or online chat

Upon consenting to take part, participants are randomised to one of eight DCEs. The example with abacavir is shown here.

0% complete

Page 1: Introduction I

Imagine you have been diagnosed with HIV.

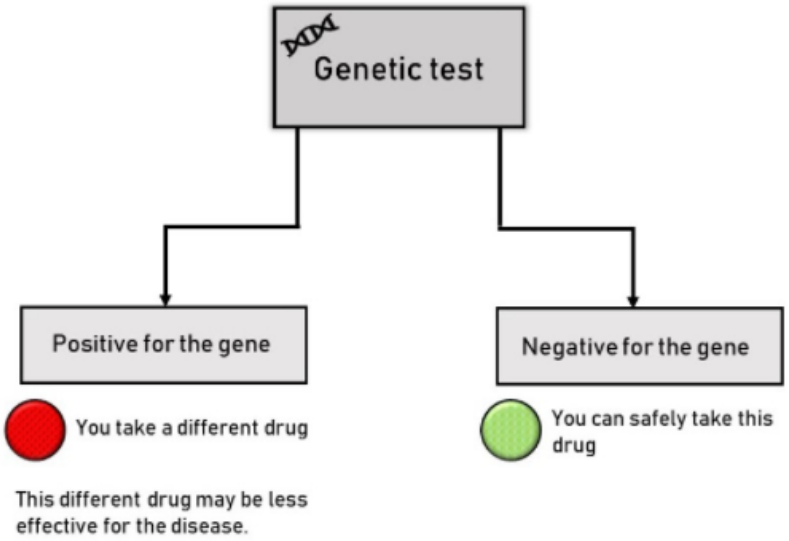
Your doctor advises you that the best treatment is a medicine called **ABACAVIR**. However, some people experience side-effects from this medicine. These can be **severe and potentially life-threatening**.

One of these is **hypersensitivity** (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

Genetic testing

We know that people with a particular type of gene in their DNA are more likely to suffer from side-effects, and **testing for this gene is now advised before prescribing abacavir in several countries.**

The test can help doctors choose a different approach, to reduce your risk of having the side-effect. People with a particular type of this gene will be prescribed a different drug, but this may be less effective for treating HIV.



Given this information, and imagining that you are in this situation, you have two options to choose from:

1. You can choose to have the gene test. If you test positive, you would receive a different drug, which might be less effective for treating HIV.
2. You can choose not to be tested, and take abacavir regardless of your risk of side-effects.

In this survey we will ask you to choose one of 2 genetic tests (Test A or Test B), with different characteristics. You can also choose not to have a test (no test).

Both tests involve a single saliva swab taken from inside the mouth. The results are available to the doctor in 1-2 days.

Submit and continue >

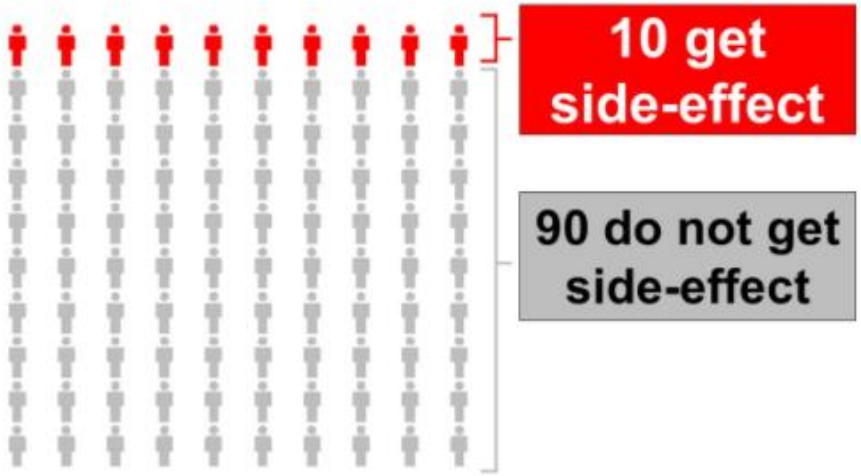
5% complete

Page 2: Introduction II

Each of the tests presented to you (Test A, Test B, or no test) is described in this survey according to 5 different characteristics, which are as follows:

1. Chance of serious side-effect from this medication

This is how many people will experience the serious side-effect. For example, 1 in 10 means that if 100 people take the drug, 10 people would experience the side-effect. This will look like this:



If you choose the 'no test' option, you will not have this information on your genetic risk of this side-effect.

2. Cost of the test to the NHS

This is how much it costs the NHS to buy the test. If you choose the 'no test' option, this is £0.

3. Use of your data for further research by universities and other researchers

Whenever you have any medical treatment, you might be asked if you want to participate in research. For these genetic tests, this would mean allowing universities and researchers access to your test results. Your test results, together with many other people's test results, would be looked at to improve medical knowledge.

This can be done in two ways. Both of these would only be done with your expressed permission.

The first is to provide your test data, but without any further information about you. Researchers would not know your name or any identifiable information. They would not be able to contact you – your data would be anonymous. There would be no way to link your data back to you.

Patient: 001

Sex: M

Ethnicity: White

Disease: HIV

Genetic test results:
Gene 1.....Positive
Gene 2.....Negative
Gene 3.....Negative

The second way asks you to give permission for researchers to request access to your medical record along with your genetic test results. This would only be for research that requires this level of detail. Allowing this gives the researchers an option to request access to much more information that might help move research along faster. They may also be able to contact you in the future if there are any clinical trials or studies that you could help by being a part of.

Patient: Steve Bennett

NHS number: 00000001

Date of birth: 01/02/75

Sex: M

Contact number: 07771112223

Ethnicity: White

Blood type: O positive

Disease: HIV

Previous medical conditions:
High blood pressure
Epilepsy
Depression

Genetic test results:
Gene 1.....Positive
Gene 2.....Negative
Gene 3.....Negative

If you choose the 'no test' option, none of your data will be used for research.

4. Number of medicines the test can be used to inform

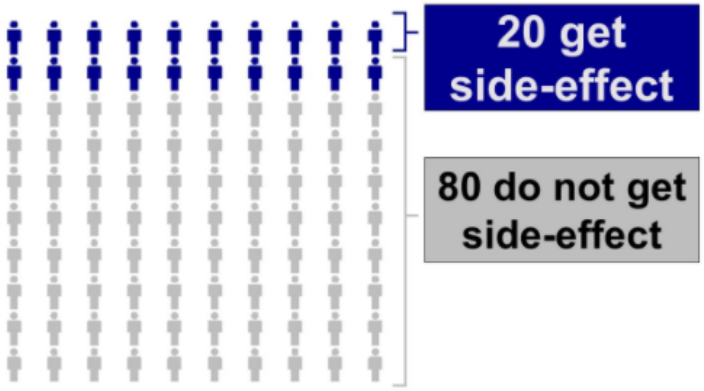
Your genetic test results tells your doctor what medicine or medicines are most suitable for you. Some genetic tests only look at one gene. With one of these single gene tests, the result is typically only used to guide the prescribing of a single medicine. However, a genetic panel test would provide enough information to cover 25 or 50 different medicines. Should you need to take any of these medicines in the future, your doctor could look up the results from the genetic panel test before prescribing.

If you choose the 'no test' option, you will not have this information.

5. Risk of *any* serious side-effect from *any* medicine over the next 10 years

A serious side-effect is one that causes sufficient concern or harm that you need to go to hospital. The diagrams show your overall chance of having a serious side-effect from **any medicine you might take in the next 10 years**, excluding the one mentioned above.

This will also look like the pictogram you saw above.



If you choose the 'no test' option, you will not have this information.

Submit and continue >

11% complete

Page 3: Question 1

These characteristics are outlined in the questionnaire below, with some variations between the choices. In each case, choose whether you would prefer to **have test A, test B, or no test**.

Take care with these. Some choices may look very similar at first glance but they are all different.

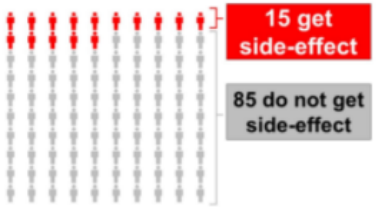
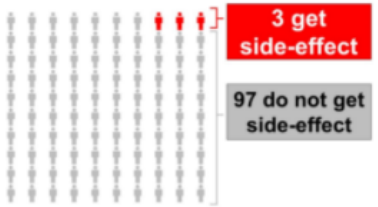
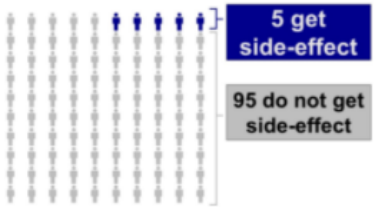
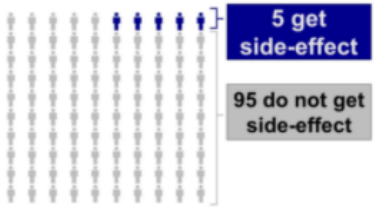
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

1	Test A	Test B	No test
Chance of serious side-effect from this medicine	15 in 100 	3 in 100 	
Use of your data for further research by universities and researchers	Yes, but no contact (anonymous)	Yes, and they can contact me (linked)	
Number of medicines the test can be used to inform	1	50	
Cost of the test to the NHS	£30	£30	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	5 in 100 	5 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

16% complete

Page 4: Question 2

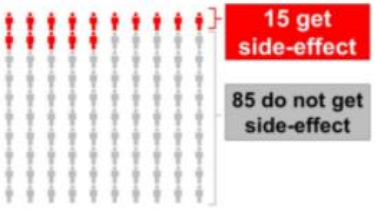
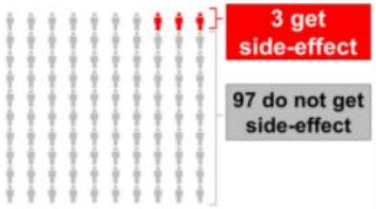
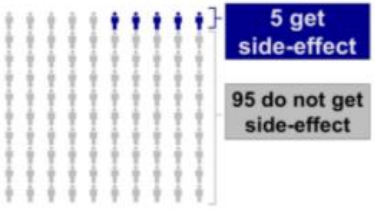
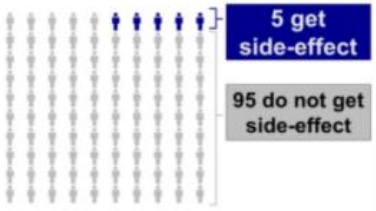
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

2	Test A	Test B	No test
Chance of serious side-effect from this medicine	15 in 100  	3 in 100  	
Use of your data for further research by universities and researchers	Yes, and they can contact me (linked)	Yes, but no contact (anonymous)	
Number of medicines the test can be used to inform	1 	50 	
Cost of the test to the NHS	£10	£50	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	5 in 100  	5 in 100  	

Which would you choose? * *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

22% complete

Page 5: Question 3

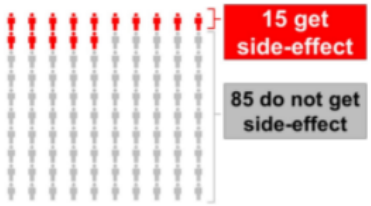
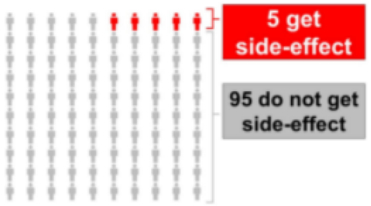
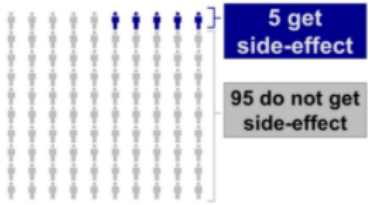
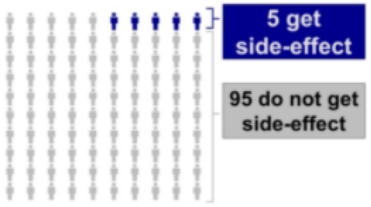
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

3	Test A	Test B	No test
Chance of serious side-effect from this medicine	15 in 100 	5 in 100 	
Use of your data for further research by universities and researchers	Yes, but no contact (anonymous)	No	
Number of medicines the test can be used to inform	25 	25 	
Cost of the test to the NHS	£10	£50	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	5 in 100 	5 in 100 	

Which would you choose? * *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue >

27% complete

Page 6: Question 4

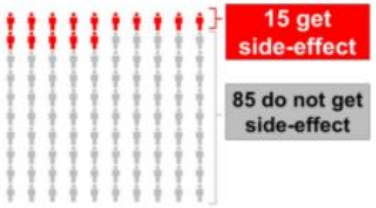
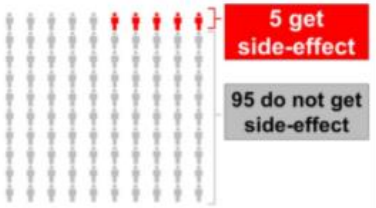
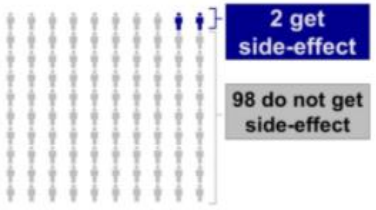
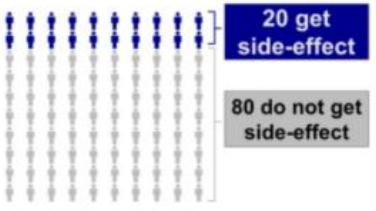
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

4	Test A	Test B	No test
Chance of serious side-effect from this medicine	15 in 100  	5 in 100  	
Use of your data for further research by universities and researchers	No	Yes, and they can contact me (linked)	
Number of medicines the test can be used to inform	25 	25 	
Cost of the test to the NHS	£30	£30	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	2 in 100  	20 in 100  	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

33% complete

Page 7: Question 5

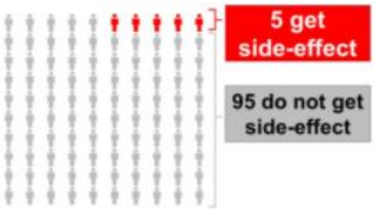
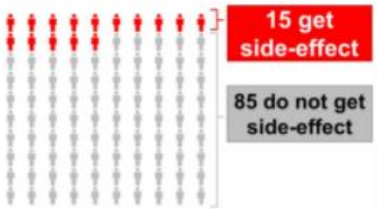
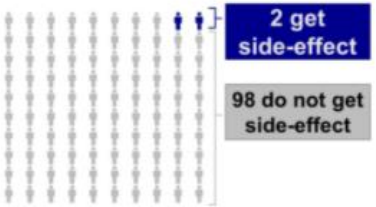
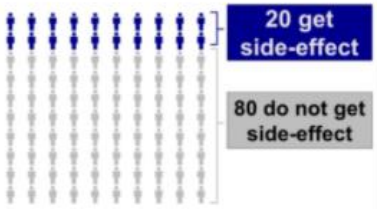
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

5	Test A	Test B	No test
Chance of serious side-effect from this medicine	5 in 100 	15 in 100 	
Use of your data for further research by universities and researchers	No	Yes, but no contact (anonymous)	
Number of medicines the test can be used to inform	1 	25 	
Cost of the test to the NHS	£10	£50	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	2 in 100 	20 in 100 	

Which would you choose? * *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

38% complete

Page 8: Question 6

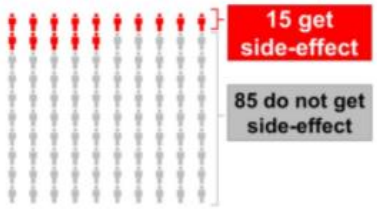
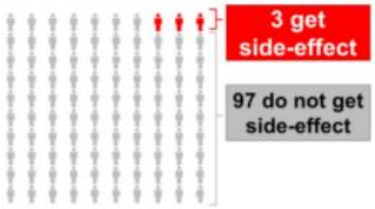
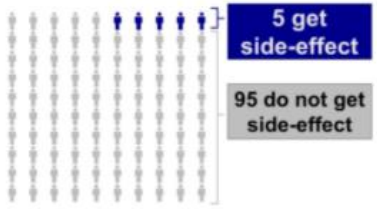
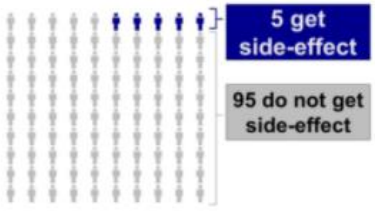
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

6	Test A	Test B	No test
Chance of serious side-effect from this medicine	15 in 100  	3 in 100  	
Use of your data for further research by universities and researchers	Yes, and they can contact me (linked)	Yes, but no contact (anonymous)	
Number of medicines the test can be used to inform	 50	 1	
Cost of the test to the NHS	£30	£30	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	5 in 100  	5 in 100  	

Which would you choose? * *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

44% complete

Page 9: Question 7

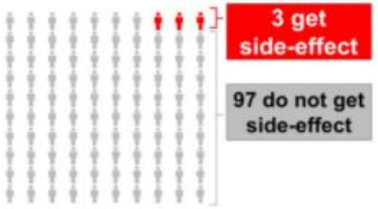
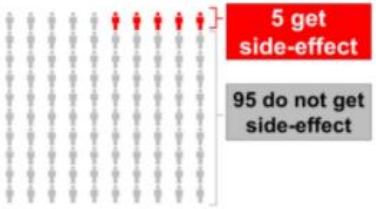
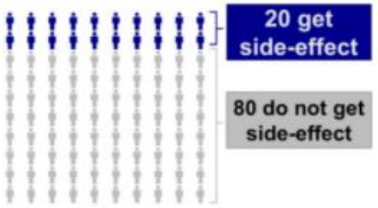
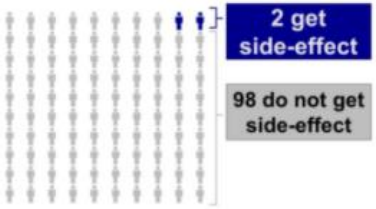
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

7	Test A	Test B	No test
Chance of serious side-effect from this medicine	3 in 100 	5 in 100 	
Use of your data for further research by universities and researchers	Yes, and they can contact me (linked)	No	
Number of medicines the test can be used to inform	1 	50 	
Cost of the test to the NHS	£30	£30	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	20 in 100 	2 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

50% complete

Page 10: Question 8

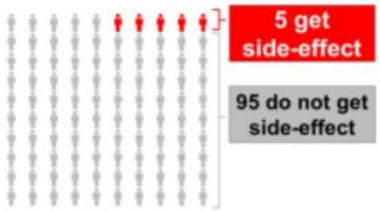
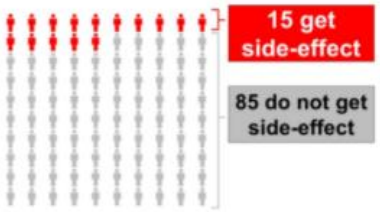
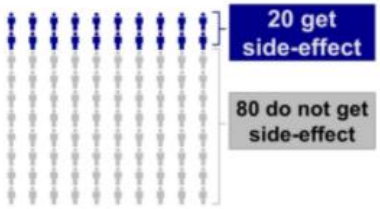
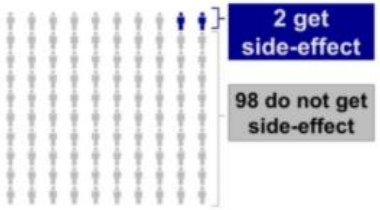
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

8	Test A	Test B	No test
Chance of serious side-effect from this medicine	5 in 100 	15 in 100 	
Use of your data for further research by universities and researchers	Yes, but no contact (anonymous)	Yes, and they can contact me (linked)	
Number of medicines the test can be used to inform	25	25	
Cost of the test to the NHS	£10	£50	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	20 in 100 	2 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

55% complete

Page 11: Question 9

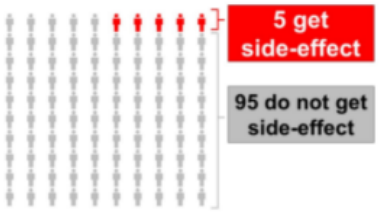
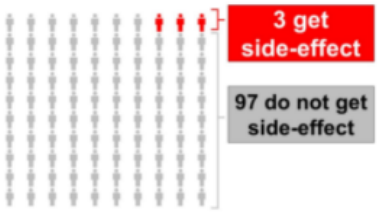
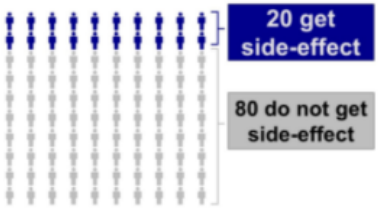
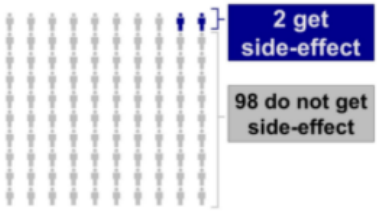
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

9	Test A	Test B	No test
Chance of serious side-effect from this medicine	5 in 100 	3 in 100 	
Use of your data for further research by universities and researchers	Yes, and they can contact me (linked)	No	
Number of medicines the test can be used to inform	25 	1 	
Cost of the test to the NHS	£50	£10	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	20 in 100 	2 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

61% complete

Page 12: Question 10

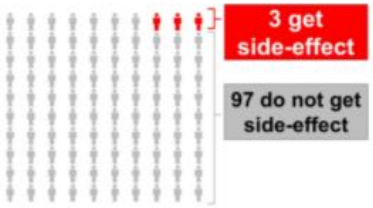
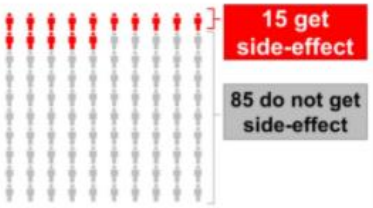
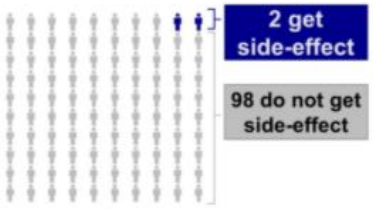
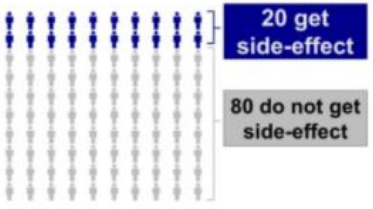
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

10	Test A	Test B	No test
Chance of serious side-effect from this medicine	3 in 100 	15 in 100 	
Use of your data for further research by universities and researchers	Yes, and they can contact me (linked)	No	
Number of medicines the test can be used to inform	50	1	
Cost of the test to the NHS	£30	£30	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	2 in 100 	20 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

66% complete

Page 13: Question 11

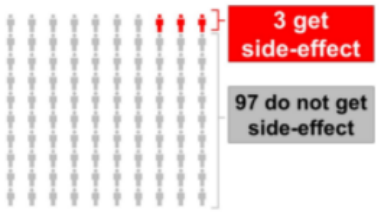
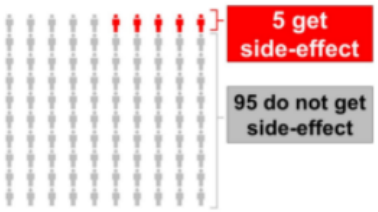
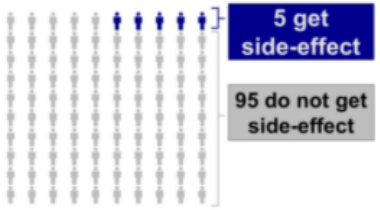
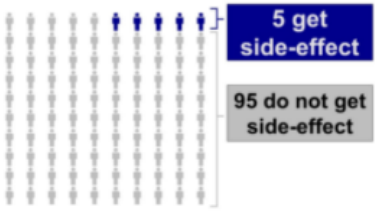
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

11	Test A	Test B	No test
Chance of serious side-effect from this medicine	3 in 100 	5 in 100 	
Use of your data for further research by universities and researchers	Yes, but no contact (anonymous)	Yes, and they can contact me (linked)	
Number of medicines the test can be used to inform	50	1	
Cost of the test to the NHS	£50	£10	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	5 in 100 	5 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

72% complete

Page 14: Question 12

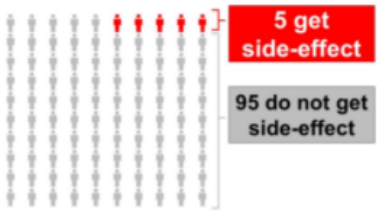
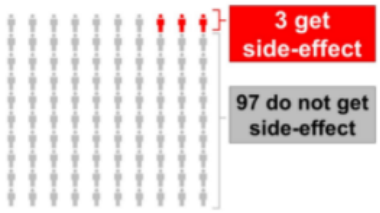
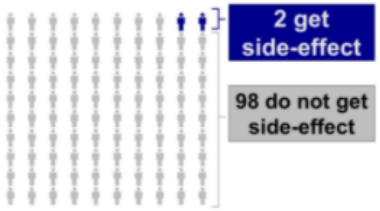
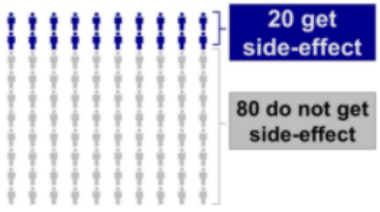
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

12	Test A	Test B	No test
Chance of serious side-effect from this medicine	5 in 100 	3 in 100 	
Use of your data for further research by universities and researchers	No	Yes, and they can contact me (linked)	
Number of medicines the test can be used to inform	50	1	
Cost of the test to the NHS	£50	£10	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	2 in 100 	20 in 100 	

Which would you choose? * *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

77% complete

Page 15: Question 13

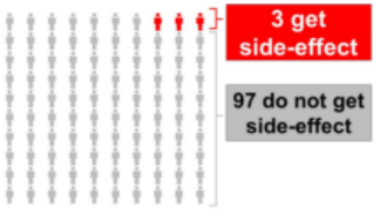
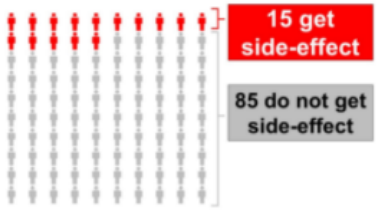
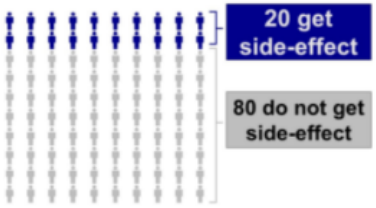
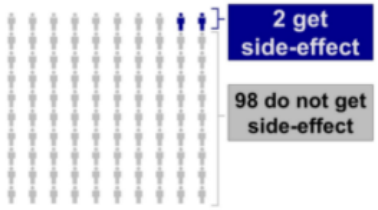
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

13	Test A	Test B	No test
Chance of serious side-effect from this medicine	3 in 100 	15 in 100 	
Use of your data for further research by universities and researchers	No	Yes, but no contact (anonymous)	
Number of medicines the test can be used to inform	1 	50 	
Cost of the test to the NHS	£10	£50	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	20 in 100 	2 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

83% complete

Page 16: Question 14

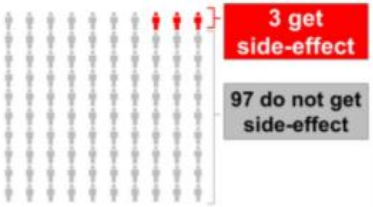
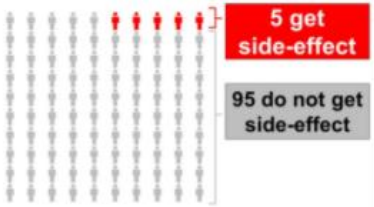
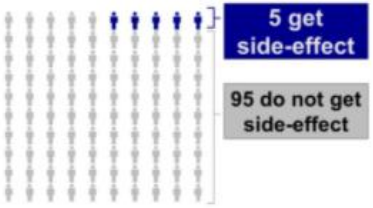
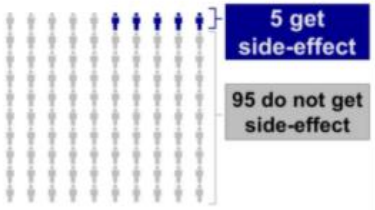
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

14	Test A	Test B	No test
Chance of serious side-effect from this medicine	3 in 100 	5 in 100 	
Use of your data for further research by universities and researchers	No	Yes, but no contact (anonymous)	
Number of medicines the test can be used to inform	 25	 25	
Cost of the test to the NHS	£50	£10	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	5 in 100 	5 in 100 	

Which would you choose? ✱ *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

88% complete

Page 17: Question 15

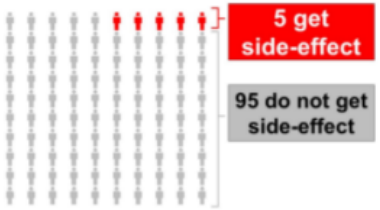
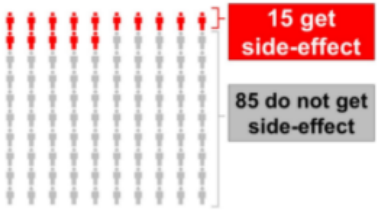
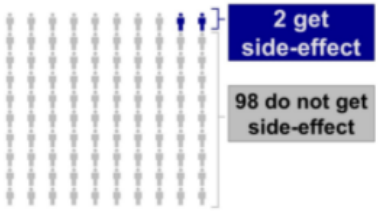
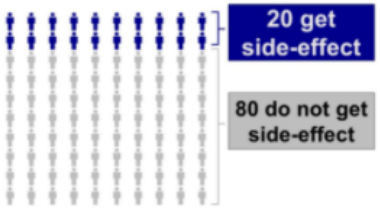
Reminder

The serious side-effect from **this medicine**:

hypersensitivity (consisting of a painful/itchy rash, nausea and vomiting, fever, and anaphylaxis – breathing problems, wheezing, and losing consciousness).

The serious side-effect from **any** medicine you might take in the **next 10 years:**

any serious side-effect that causes sufficient harm or concern that you need to go to hospital.

15	Test A	Test B	No test
Chance of serious side-effect from this medicine	5 in 100 	15 in 100 	
Use of your data for further research by universities and researchers	Yes, but no contact (anonymous)	No	
Number of medicines the test can be used to inform	1 	25 	
Cost of the test to the NHS	£30	£10	
Risk of serious side-effect from any medicine over the next 10 years, *excluding this medicine*	2 in 100 	20 in 100 	

Which would you choose? * *Required*

- ○ Test A
- ○ Test B
- ○ No test

Submit and continue ›

94% complete

Page 18: Final questions

What is your age group?

- ○ 18 - 24
- ○ 25 - 34
- ○ 35 - 44
- ○ 45 - 54
- ○ 55 - 64
- ○ 65+

What is your gender?

- ○ Female
- ○ Male
- ○ Another
- ○ Prefer not to answer

Have you ever had a genetic test?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Prefer not to answer

Have you suffered from the illness described in this survey?

- ○ Yes
- ○ No
- ○ Don't know
- ○ Prefer not to answer

How difficult did you find this survey to complete, on a scale of 1 (not difficult at all) to 10 (almost impossible) ?

Please select

Do you have any comments on this survey? (please do not include any identifiable information here)

Finish ✔

100% complete

Final page

Thank you for completing this survey.

Thank you for completing this survey. Your data has been stored anonymously, and it is not possible to identify you or to remove it from the servers. However, if you have any concerns, you can contact

danielle.johnson@liverpool.ac.uk or

ethics@liverpool.ac.uk

If you have any particular concerns about HIV you may find it helpful to contact Terrence Higgins Trust: 0808 802 1221 (10am-6pm weekdays, 10am-1pm weekends) or info@tht.org.uk

You can also contact the researchers directly.

For 24/7 mental health support, you can contact Samaritans: 116 123 (24/7) or email jo@samaritans.org

Click here to submit your responses

Chapter 7

7.1 Stata code for DCE analysis

```
**This is correct for ABACAVIR
ssc install outreg2

clear
cd "M:\Stata"

capture log close
log using abacavirwtp.log, replace text
set more off

*import, using first row as variable names
import excel using datamatrix_abacavir.xlsx , firstrow


*check first 2 rows look right
list in 1/2

*run the model
xtlogit pref asc_no adr_today_1 adr_today_2 privacy_yes1 privacy_yes2 medsno cost future_adr_1 future_adr_2, re i
(personid)

*export results to excel
outreg2 using abacavirresults, excel

**save here as abacavir_boot.dta**

*using output of the previous abacavir run (abacavir_boot.dta)
use "M:\Stata\abacavir_boot.dta"
bootstrap, saving("M:\Stata\abacavir_boot_results_mean.dta") reps(1000) seed(123) : xtlogit pref asc_no adr_today_1
adr_today_2 privacy_yes1 privacy_yes2 medsno cost future_adr_1 future_adr_2, re i (personid)

generate pref_adr_today_0 = -1*(pref_b_adr_today_1+pref_b_adr_today_2)
generate pref_privacy_no = -1*(privacy_yes1+privacy_yes2)
generate pref_future_adr_0 = -1*(pref_b_future_adr_1+pref_b_future_adr_2)
```

```
export excel using "M:\Stata\abacavir_boot_results.xls", firstrow(variables)
log close
```

7.2 Data matrices for each DCE

See https://www.dropbox.com/sh/gp40k9go4qgrmnr/AAB7ZXZqM3ImSmA3YUbyqIZva?dl=0

7.3 Bootstrapped beta-coefficients for each DCE

See https://www.dropbox.com/sh/oygat71gu9ch0d3/AACPdb_2y3ujNsAcscJ60kQHa?dl=0

7.4 Utility modelling for each DCE

See https://www.dropbox.com/sh/69eka4kmyx8e680/AADgWAMGzpPYkPHAcw8UJUq_a?dl=0

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