表❶ SSRIの体内薬物動態的パラメータ

	生体利用率 (%)	血漿蛋白結合性 (%)	分布容積 (L/kg)	クリアランス (L/h)	半減期 平均 (h)	半減期 範囲 (h)	定常状態の平均血中濃度(ng/mL)
フルボキサミン	＞53	77	＞5	80 (33〜220)	15	9〜28	20〜500
パロキセチン	＞64	93	17	36〜167	18	7〜65	10〜600
セルトラリン	＞44	98	25	96	26	22〜36	20〜200
fluoxetine	80	95	25	10〜36	45	24〜144	90〜300

(DeVane CL, 1998[1]より改変引用)

表❷ SSRIの主要な代謝酵素

親化合物	主要な代謝産物	代謝酵素
フルボキサミン	特になし	CYP1 A2，CYP2D6
パロキセチン		CYP2D6
セルトラリン	desmethylsertraline	CYP2C9，CYP3 A4
fluoxetine		CYP2C9（CYP3 A4，CYP2D6）

(Greenblatt DJ *et al*, 1998[2] より改変引用)

フルボキサミンのまま体循環に入る割合は約53％とされている[3]．フルボキサミン25，50，100 mgを健康成人に1回投与した場合の最高血清中濃度（Cmax）は，それぞれ9.17，18.0，38.1 ng/mLとほぼ直線的に増加し，最高血清中濃度到達時間（Tmax）は2〜8時間（平均5時間）と報告されている．しかしフルボキサミン100，200，300 mgという高用量を10日間反復投与した結果，血中濃度がそれぞれ88，283，546 ng/mLと非直線的に増加したという報告もある[4]．

フルボキサミンは他の三環系抗うつ薬や抗精神病薬と同様に，血中よりも肺・肝・腎などの主要な臓器でより高い濃度を示すことが動物実験で示されている．このことはフルボキサミンの疎水性が高いためであり，透析患者などへのフルボキサミンの補充が必要でないことを意味している．フルボキサミンの分布容積は約5L/kgであり，特定の臓器への異常な蓄積性は認められていない[3]．

フルボキサミンの血漿蛋白結合性は約77％であり，すべてのSSRI中最も低いとされている．高蛋白結合性の薬物同士の併用は，非結合型の血中薬物濃度を上昇させるが，フルボキサミンにおいては蛋白結合を介した他の薬物との相互作用は比較的少ないと考えられる[3]．

^{14}C-ラベル体を用いたフルボキサミン経口投与試験によれば，投与後71時間までの尿中放射能総排泄率は平均94％であり[4]，このうちフルボキサミンの未変化体は4％以下であった[3]．半減期は約9〜28時間であり[1]，投与量による影響はあまりないものと考えられている．仮に投与量を変更した場合，新たに定常状態に達するには約5日間が必要であると考えられる[5]．

わが国のフルボキサミン第I相試験の結果では，25，50，100，200 mg単回投与におけるCmaxはそれぞれ9.14，17.25，43.77，91.81 ng/mL，Tmaxはそれぞれ5.17，4.67，3.50，4.67時間であり，75 mgの6日間反復投与では，3日間で定常状態（10.6 ng/mL）に達したと報告されている[6]．また4週間の投与試験においても蓄積性は認められず，平均100 mgの投与量の範囲では用量依存性に血中濃度が増加していた[7]．

フルボキサミンの代謝にはチトクロームP450（CYP）2D6および1 A2が関与するとされ

ている（図❶-①）[8]．CYP1A2の関与については，喫煙がCYP1A2を誘導すること，フルボキサミン内服中の喫煙者においてはフルボキサミン血中濃度が非喫煙者にくらべて有意に低いことから説明されている[3)9)]．また，CYP2D6についてはデブリソキンやデキストロメトルファンを試験薬として用いた研究において，フルボキサミンの薬物動態にCYP2D6の関与を示唆した報告がある[10)]．

②高齢者

フルボキサミン50，100mgを65歳以上の高齢者に単回投与した場合，Cmaxが約40%上昇したという報告があり，同じ投与量で定常状態にある高齢者では，半減期が130～160%延長したとされている[11)]．

わが国での高齢者（65歳以上）うつ病・うつ状態患者に対する臨床試験においても，平均の血中濃度が増加する傾向が認められている[12)]．この試験ではより重篤な副作用は認められなかったものの，高齢者においてはより低用量からの慎重な薬剤投与が必要であると考えられる．

③肝機能・腎機能障害者

肝硬変などの肝機能障害を有する患者では肝におけるフルボキサミンのクリアランスが30%ほど減少することが示唆されていることから，血中濃度が上昇する可能性が予測され，肝機能障害の患者にフルボキサミンを投与する場合には低用量から開始すべきである．一方，血清アルブミンの減少がフルボキサミンの薬物動態に与える影響は比較的少ないとされている[3)4)]．

腎機能障害を有する患者においてはフルボキサミンの血中濃度が変化しないという報告があるが，フルボキサミンの代謝産物のほとんどが尿中に認められること，高度の腎機能障害が肝機能を低下させてしまうことなどを考慮して，腎機能障害を有する患者においても低用量からの投与が適当であろう[3)]．

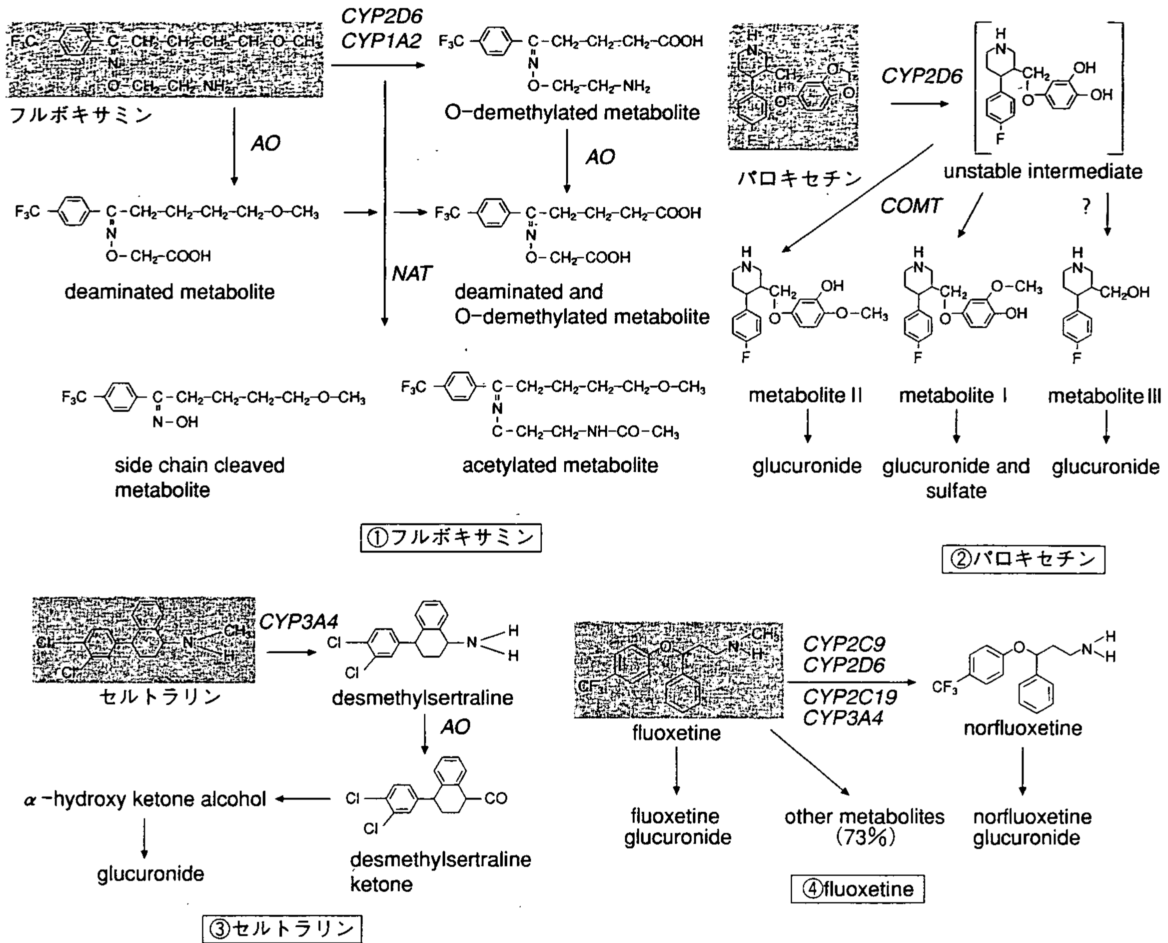
2）パロキセチン

①吸収・分布・代謝・排泄

^{14}C-ラベル体を用いたパロキセチンの健常成人への単回投与は，消化管からほぼ完全に吸収される[13)]．パロキセチンの分布容積は3～12L/kgでありフルボキサミンの分布容積（5L/kg）にほぼ等しい[8)]．またパロキセチンのヒト血漿蛋白結合性は血中濃度100，400ng/mLでそれぞれ93，95%であり，フェニトイン，ワルファリンの血漿蛋白結合性に影響を与えないとされている[14)]．

パロキセチンの代謝には少なくとも2つの経路が関与しており（図❶-②），一つはCYP2D6の関与する飽和型の代謝経路であり，もう一つはCYP2D6以外のCYPアイソエンザイムによる代謝経路である．パロキセチンでは薬物動態の非線形性が報告されているが，CYP2D6以外の代謝経路が別に存在していることもこのことに関連している[15)]．また*CYP2D6*遺伝子の変異アレルおよびパロキセチンの用量が血中濃度に与える影響が報告されており，パロキセチンの血中濃度について変異アレルを有する群と有さない群とで比較した場合，低用量（10mg/日）では変異アレルをもつ群で血中濃度が有意に高かったとされている[16)]．

パロキセチン30mgを30日間経口投与した場合，約10日間で定常状態に達し，平均Cmax，Tmax，Cmin（最低血清中濃度），半減期はそれぞれ61.7ng/mL，5.2時間，30.7ng/mL，21.0時間と報告されている[17)]．CmaxおよびCminの値はパロキセチン単回投与の報告から予測される値にくらべて，それぞれ6倍，14倍と高い．前述したパロキセチン薬物動態の非線形性に関しては，投与量で補正した薬物血中濃度時間曲線下面積（area under the drug concentration time curve：AUC）比が，西欧人で0.8～7.6，日本人



図❶ 各種 SSRI 代謝動態

(Hiemke C *et al*, 2000[8] より改変引用)

で 1.1～5.9 であり，1 をほとんど超えていること，健常成人（日本人）にパロキセチン 10，20，および 40 mg を単回投与したときの Cmax および AUC は，投与量増加の割合を上回って増加していることなどからも示唆されている[13)15)]．このような非線形性を示す理由として，パロキセチンの代謝酵素 CYP2D6 の飽和または自己阻害（self inhibition）が関与していることが指摘されている[14)]．

パロキセチンは酸化，抱合を受けて代謝されるが，その代謝産物は薬理学的活性をほとんどもたない．30 mg を 10 日間経口投与されたパロキセチンの約 64%が尿中に（うち 2%が未変化体），約 36%が糞便中に（うち未変化体は 1%以下）認められている[18)]．

②高齢者

加齢による影響は，パロキセチンの薬物動態に大きな変化を与えることはなく，臨床的にも血圧や脈拍，臨床検査や心電図などで問題となる変化はみられないとする報告がある[19)20)]．しかし若年者と比較してパロキセチンの Cmin が 70～80%増加したという報告などもあり[14)]，パロキセチンにおいても高齢者への投与は低用量から慎重におこなうべきと考えられる．

③肝機能・腎機能障害者

わが国の研究においては，軽微な肝機能・腎機能障害患者に対するパロキセチンの薬物動態は健常者とくらべて有意な差は認められなかった[19]．しかしクレアチニン・クリアランスが30〜60 mL/分の患者および肝機能障害の患者においてパロキセチンの血中濃度が約2倍，クレアチニン・クリアランス30 mL/分以下の患者では約4倍に上昇するという報告もある[14]．

3）その他のSSRI

①セルトラリン

セルトラリン単回投与によるわが国の第I相試験では，投与後約6〜9時間で最高血中濃度に達し，半減期は約23〜24時間であり，1日1回投与が可能であることが示唆されている[21]．Cmax，AUCもほぼ用量依存的に増加し，100 mgの反復投与試験では4〜7日で定常状態（40.4〜43.9 ng/mL）に達した[22]．また薬物動態に関しては食事の影響を受けないとされている[23]．

経口投与されたセルトラリンはおもに肝臓で代謝される．この代謝にはCYP3A4やCYP2C9が関連していることが示唆されており[24]（図❶-③），CYP2D6の関与は大きくないといわれている[25]．主要な代謝産物にN-desmethylsertralineがあり，この半減期は62〜104時間，薬効はセルトラリンの1/10以下であると考えられている[26]．

放射性物質でラベルされたセルトラリンを経口投与した場合，投与後9日目までの尿中放射能総排泄率は40〜45%であり，未変化体は認められない．糞便中への排泄率は40〜45%であり，うち12〜14%がセルトラリンの未変化体であった[27]．また，セルトラリンの血漿蛋白結合性は約98%と高く，他の蛋白結合性が高い薬物との相互作用に注意が必要である[28]．

高齢者では若年者と比較してセルトラリンのクリアランスが40%減少する．また高齢者うつ病患者（65歳以上）に対する臨床試験の結果では，若年者と比較して半減期が延長する傾向が認められた[29]．

肝機能障害患者においては半減期が延長し，Cmax, AUCも増加したという報告があるが，腎機能障害患者におけるセルトラリンの薬物動態は明らかでない[27]．

②fluoxetine

fluoxetineはR-fluoxetineとS-fluoxetineといった鏡像異性体を等分にもつ混合物であり，S体はR体にくらべて血中からの消失速度が遅いため，定常状態ではS体が優位である[30]．R,S-fluoxetineはそれぞれ肝臓で脱メチル化され，R,S-norfluoxetineに代謝される．R,S-fluoxetine，R,S-norfluoxetineともに同程度のセロトニン阻害作用を有するが，R-norfluoxetineはS-norfluoxetineの1/22の活性しか有さない[31]．

fluoxetineを40 mg経口投与した場合，Tmaxは6〜8時間，Cmaxは15〜55 ng/mLと報告されており，吸収に対する食事の影響は少ないと考えられている[30]．

fluoxetine，norfluoxetineの半減期は，単回投与の場合にそれぞれ1〜3日，4〜6日と比較的長い．継続投与の場合でともに4〜6日と比較的長い．このため，fluoxetine中断後も数週間は体内に薬物が残存し，他の薬物との相互作用に注意が必要である[32]．

fluoxetineの主要な代謝酵素はCYP2C9であり，その他にCYP3A3，CYP3A4も関与しているとされている[33]（図❶-④）．

これまでの報告によると，高齢者においては若年者と比較した場合にfluoxetineの薬物動態に有意な変化はみられないようである[34]．また肝硬変患者において，fluoxetineの半減期が2〜3日から平均7.3日に延長したという報告があり[21]，腎機能障害者ではfluoxetine 20 mgを2カ

月間投与しても fluoxetine, norfluoxetine の血中濃度は健常者と比較しても有意な差はなかったとされている[35]．

おわりに

SSRI の薬物動態と代謝についてフルボキサミン，パロキセチンを中心に概説した．わが国では，フルボキサミンが 1999 年に導入されて以来，従来の三環系抗うつ薬と比較して副作用が少なく，治療効果も同等であるなどの理由から，現在では SSRI がうつ病治療の第一選択薬として使用されている．しかしその使用法については，臨床症状や副作用の出現などを評価することで用量の調整や他剤への変更などが判断されており，TDM などの客観的な指標により体内薬物動態などを考慮して薬剤選択をおこなうなどの有用性についてはまだ認められていない．このような情報の蓄積や追証が今後の個別化薬物医療の実現にとって重要だと思われ，臨床に携わる者としては少なくとも体内での薬物動態を十分に理解し，SSRI の利点をより引き出せるようにしておくことが必要である．

（須貝拓朗/澤村一司/染矢俊幸）

文　献

1) DeVane CL：Differential pharmacology of newer antidepressants. *J Clin Psychiatry* 59 (suppl 20)：S85-S93, 1998
2) Greenblatt DJ：Drug interactions with newer antidepressants：role of human cytochrome P450. *J Clin Psychiatry* 59 (suppl 15)：S19-S27, 1998
3) DeVane CL, Gill HS：Clinical pharmacokinetics of fluvoxamine：applications to dosage regimen design. *J Clin Psychiatry* 58 (suppl 5)：S7-S14, 1997
4) PDR：*Physicians' Desk Reference*, 1998 (52nd edition), ed. by J. Paul Folsman, Medical Economics Company, Oradell, NJ, 1998, pp.2891-2894
5) Lam YW, Gaedigk A, Ereshefsky L *et al*：CYP2D6 inhibition by selective serotonin reuptake inhibitors：analysis of achievable steady-state plasma concentrations and the effect of ultrarapid metabolism at CYP2D6. *Pharmacotherapy* 22：1001-1006, 2002
6) 石郷岡純：選択的セロトニン再取り込み阻害薬 SME3110（fluvoxamine maleate）の第 I 相試験．臨床評価 21：441-490，1993
7) 岡五百理：選択的セロトニン再取り込み阻害薬 SME3110（fluvoxamine maleate）のうつ病，うつ状態に対する臨床評価―長期投与試験―．臨床医薬 12：471-487，1996
8) Hiemke C, Hartter S：Pharmacokinetics of serotonin reuptake inhibitors. *Pharmacol Ther* 85：11-28, 2000
9) Dudek D, Zieba A, Siwek M *et al*：Selective serotonin reuptake inhibitors—current knowledge. *Psychiatr Pol* 38：507-524, 2004
10) Carrillo JA, Dahl ML, Svensson JO *et al*：Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. *Clin Pharmacol Ther* 60：183-190, 1996
11) Spina E, Scordo MG：Clinically significant drug interactions with antidepressants in the elderly. *Drugs Aging* 19：299-320, 2002
12) 筒井末春：選択的セロトニン再取り込み阻害薬 SME3110（fluvoxamine maleate）の高齢者のうつ病，うつ状態に対する臨床試験．臨床薬理 12：261-275，1996
13) 坂本孝司，井之川芳之，成田裕保：塩酸パロキセチンの第 I 相臨床試験（第 6 報）．薬理と治療 28（suppl）：S111-S118，2000
14) PDR：*Physicians' Desk Reference*, 1998 (52nd edition), ed. by J. Paul Folsman, Medical Economics Company, Oradell, NJ, 1998, pp.2851-2856
15) Sindrup SH, Brosen K, Gram LF：Pharmacokinetics of the selective serotonin reuptake inhibitor paroxetine. *Clin Pharmacol Ther* 51：288-295, 1992
16) Sawamura K, Suzuki Y, Someya T：Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine. *Eur J Clin Pharmacol* 60：553-557, 2004
17) 村崎光邦，高橋明比古，井之川芳之：塩酸パロキセチンの第 I 相臨床試験（第 2 報）．薬理と

治療 28（suppl）：S37-S46, 2000
18) Kotzailias N, Marker M, Jilma B：Early effects of paroxetine on serotonin storage, plasma levels, and urinary excretion：a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 24：536-539, 2004
19) 小林一広，村崎光邦，稲見充昭：選択的再取り込み阻害薬塩酸パロキセチンの肝機能・腎機能低下のうつ病患者における薬物動態試験．薬理と治療 28（suppl）：S237-S252, 2000
20) Golden RN：Efficacy and tolerability of controlled-release paroxetine. *Psychopharmacol Bull* 37（suppl 1）：S176-S186, 2003
21) 上島国利：塩酸セルトラリン（CP-51, 974-1）第 I 相試験―単回投与試験―．神経精神薬理 19：395-423, 1997
22) 上島国利：塩酸セルトラリン（CP-51, 974-1）第 I 相試験―反復投与試験―．神経精神薬理 19：425-447, 1997
23) 上島国利：塩酸セルトラリンの薬物動態に及ぼす食事の影響．神経精神薬理 19：461-470, 1997
24) Reis M, Aberg-Wistedt A, Agren H *et al*：Serum disposition of sertraline, N-desmethylsertraline and paroxetine：a pharmacokinetic evaluation of repeated drug concentration measurements during 6 months of treatment for major depression. *Hum Psychopharmacol* 19：283-291, 2004
25) Hamelin BA：The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 60：512-521, 1996
26) DeVane CL, Liston HL, Markowitz JS：Clinical pharmacokinetics of sertraline. *Clin Pharmacokinet* 41：1247-1266, 2002
27) PDR：*Physicians' Desk Reference,* 1998（52nd edition), ed. by J. Paul Folsman, Medical Economics Company, Oradell, N J, 1998, pp.2229-2234
28) MacQueen G, Born L, Steiner M：The selective serotonin reuptake inhibitor sertraline：its profile and use in psychiatric disorders. *CNS Drug Rev* 7：1-24, 2001
29) 上島国利：塩酸セルトラリンの高齢者うつ病に対する臨床試験―高齢者に対する臨床的有用性および薬物動態の検討―．神経精神薬理 19：569-585, 1997
30) PDR：*Physicians' Desk Reference,* 1998（52nd edition), ed. by J. Paul Folsman, Medical Economics Company, Oradell, NJ, 1998, pp.859-863
31) Henry ME, Schmidt ME, Hennen J *et al*：A comparison of brain and serum pharmacokinetics of R-fluoxetine and racemic fluoxetine：A 19-F MRS study. *Neuropsychopharmacology* 30：1576-1583, 2005
32) Wernicke JF：Safety and side effect profile of fluoxetine. *Expert Opin Drug Saf* 3：495-504, 2004
33) Hall J, Naranjo CA, Sproule BA *et al*：Pharmacokinetic and pharmacodynamic evaluation of the inhibition of alprazolam by citalopram and fluoxetine. *J Clin Psychopharmacol* 23：349-357, 2003
34) Gury C, Cousin F：Pharmacokinetics of SSRI antidepressants：half-life and clinical applicability. *Encephale* 25：470-476, 1999
35) von Moltke LL：Human cytochromes mediating N-demethylation of fluoxetine *in vivo*. *Psychopharmacology* 132：402-407, 1997

Mapping translational research in the age of theragnostics: from molecular markers to personalized drug therapy

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Translational research is frequently used in the bioscience literature to refer to the translation of basic science into practical applications at the point of patient care. With the introduction of theragnostics, a new medical subspecialty that fuses therapeutics and diagnostic medicine with the goal of providing individualized pharmacotherapy, we suggest that the focus of translational research is shifting. We identify two bottlenecks or gaps in translational research for theragnostics: GAP1 translation from basic science to first-in-human proof-of-concept; and GAP2 translation from clinical proof-of-concept to development of evidence-based personalized treatment guidelines. GAP1 translational research in theragnostics is usually performed in traditional craft-based studies with small sample sizes and led by independent academic or industry researchers. In contrast, GAP2 translational investigations typically rely on large research consortiums and population-based biobanks that couple biomarker information with longitudinal 'real-life' observational data on a broad range of pharmacological phenotypes. Despite an abundance of research on the use of biobanks in disease gene discovery, there has been little conceptual work on whether and to what extent population biobanks can be utilized for translating genomics discoveries to practical treatment guidelines for theragnostic tests.

Keywords: biobanks, bioethics, biomarkers, General Clinical Research Center, theragnostics, personalized medicine, translational clinical research

future medicine

For biomedicine to improve human health, scientific discoveries must be 'translated' into applications at the point of patient care [101]. These applications can be information generating (for example, genetic tests that aid in prediction of disease risk or the individualization of drug therapy) or therapeutic (for example, new drug therapies and medical devices). Research that works between or at the interface of these two poles, that is molecular/preclinical investigations and practical applications in the clinic, is often referred to as 'translational research'.

As an applied science, translational research has a prominent focus on clinically-relevant product development. In the present age of knowledge-based economies [1,2], translational research is increasingly visible and highly sought after by academics, research funding agencies and pharmaceutical or biotechnology industries. However, despite its frequent use in the scientific literature there has been little conceptual work that maps out the process of translational research. For example, is such research a multistage process with several qualitatively different subcomponents? And what does translational research contribute in the context of recent trends towards developing personalized drug therapies? Furthermore, we suggest that translational research is currently being reshaped by the introduction of theragnostics, a term denoting the fusion of therapeutics and diagnostics [3].

Theragnostics indicates a fundamental transformation in pharmaceutical research and medical therapeutics, that is, a move towards codevelopment, and by extension, coprescription of diagnostic tests and drugs to individualize treatment regimens. Unlike routine clinical chemistry (for example., plasma electrolyte measurements) or technology-driven biomarker approaches (for example., genomics), theragnostics does not focus on a single technology platform or marker set, such as blood biochemistry or genetic polymorphisms. Instead, theragnostics relies on an integration of technologies for gathering information from different levels of the biological hierarchy. Thus, a theragnostic approach might include not only pharmacogenomic tests [4] to identify the hereditary basis for individual or population variability in drug effects (whether based on genotype or gene expression), but also include proteomic [5] and metabolomic [6] tests to discern, respectively, the cellular proteins and metabolites formed and degraded under genetic or (patho)physiological influences (Figure 1). For example, trastuzumab (Herceptin®) is a monoclonal antibody directed at the human epidermal growth factor receptor 2 (*HER2*) for use in patients with breast cancer who are *HER2*-positive. Trastuzumab is widely claimed as one of the first generation of personalized medicines, because the drug is prescribed together with a theragnostic test to detect *HER2*

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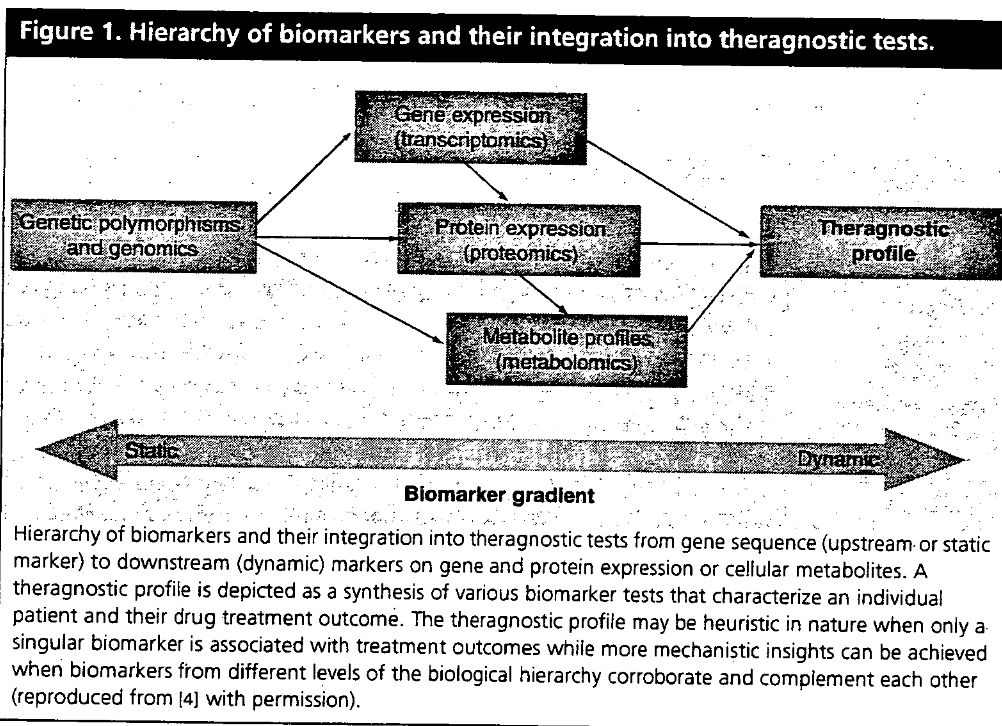
Figure 1. Hierarchy of biomarkers and their integration into theragnostic tests.



Hierarchy of biomarkers and their integration into theragnostic tests from gene sequence (upstream or static marker) to downstream (dynamic) markers on gene and protein expression or cellular metabolites. A theragnostic profile is depicted as a synthesis of various biomarker tests that characterize an individual patient and their drug treatment outcome. The theragnostic profile may be heuristic in nature when only a singular biomarker is associated with treatment outcomes while more mechanistic insights can be achieved when biomarkers from different levels of the biological hierarchy corroborate and complement each other (reproduced from [4] with permission).

overexpression; the test itself can use a variety of methods including gene (i.e., pharmacogenomic) and/or protein expression [7,8] Theragnostics is thus a more holistic approach (and not a singular technology) to diagnosis and therapy selection than has traditionally been the case in biomarker research or medical practice.

This paper identifies and differentiates two bottlenecks or gaps (hereafter referred to as GAP1 and GAP2) in the conduct of translational research in the emerging field of theragnostics. There is a major gap, GAP1, in the translation of basic science discoveries to first-in-human (FIH) proof-of-concept [9]. A second serious gap, GAP2, occurs in the transition from clinical proof-of-concept to the development of appropriate treatment guidelines and science policy. We suggest that resolution of these bottlenecks or gaps requires distinct research aims, resources and study designs. For example, research directed at GAP1 may require focused small sample size academic or industry-sponsored studies. In contrast, GAP2 translational research would require large-scale longitudinal population databases on observational 'real-life' treatment outcomes and core technical biomarker competency to explain variability in drug effects [10–12]. These gaps in translational research are collectively sufficiently important for the US FDA to have the view that, "the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process" [11].

'Unpacking' translational research in theragnostics

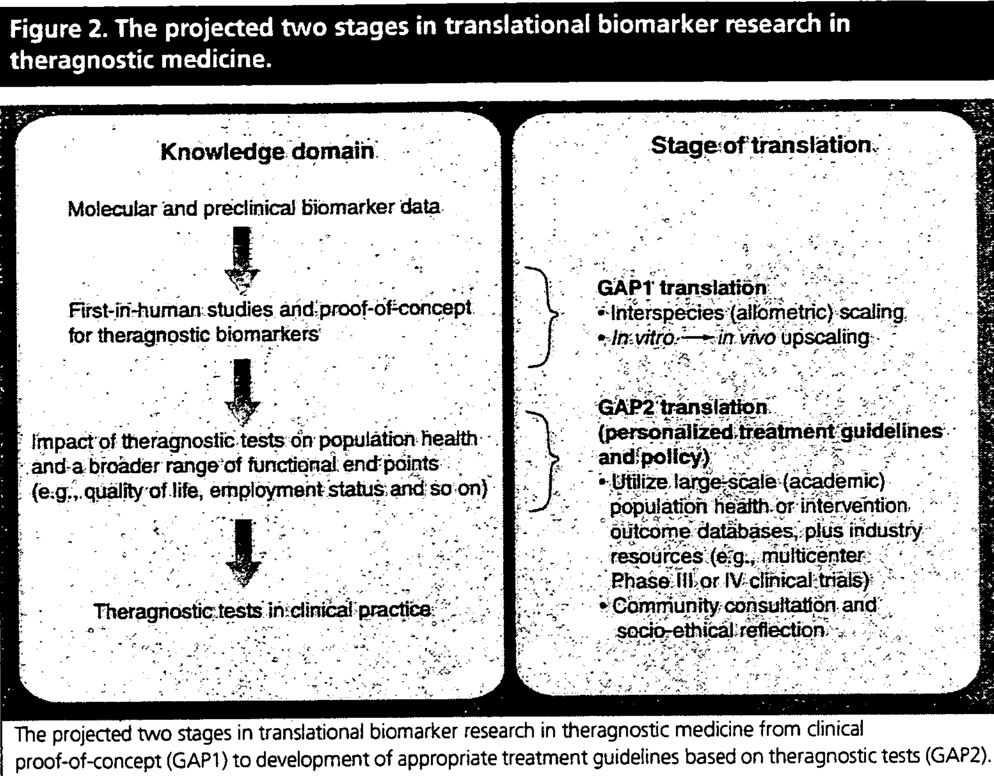
GAP1: translation from basic science to first-in-human proof-of-concept

The need for GAP1 translational research in theragnostics stems from three fundamental considerations:

- The obvious interspecies differences in pharmacokinetic pathways and molecular drug targets;
- The inevitable biological contrasts between the inbred laboratory animals with a homogenous genetic background and outbred human populations who exhibit marked genetic variability and exposure to a diverse array of social and environmental factors;
- The need for scaling up molecular observations *in vitro* to an integrated systems biology context in the whole (human) organism *in vivo* (Figure 2).

FIH proof-of-concept studies play a pivotal role in bridging the divide (i.e., GAP1) between preclinical biomarker research and large-scale population-based clinical investigations for theragnostic test development and validation. Despite their small sample size and limited scope

Figure 2. The projected two stages in translational biomarker research in theragnostic medicine.



The projected two stages in translational biomarker research in theragnostic medicine from clinical proof-of-concept (GAP1) to development of appropriate treatment guidelines based on theragnostic tests (GAP2).

of inquiry (usually less than 100 subjects per study), FIH studies make an important contribution as a first step in proof-of-concept and knowledge translation between *in vitro* and *in vivo* approaches, or more broadly, in extrapolation of data from animal models to the whole human organism. For example, clinical trials selectively testing patients with certain genetic subtypes of drug targets previously shown to confer an increased likelihood of response can facilitate proof-of-concept decisions on whether and to what extent a new molecular entity (NME) is a viable therapeutic candidate. An inadequate clinical response to an NME in such enriched samples may serve as an early indication of possible therapeutic failure in the general patient population [9].

A glance at leading clinical pharmacology and pharmacogenomic journals attests to the proliferation of genotype–phenotype correlative studies over the past 10 years [13,14]. Many of these studies fall under the GAP1 translational biomarker research; they often have small sample sizes. In an attempt to develop, implement, and disseminate a public genotype–phenotype resource, Stanford University (CA, USA), with funding from the NIH, established the Pharmacogenetics & Pharmacogenomics Knowledgebase (PharmGKB) [102]. This database is part of the NIH Pharmacogenetics Research Network (PGRN), a nationwide collaborative research consortium. The PharmGKB stores data regarding genetic sequence variation and their association with drug-related phenotypes, and provides methods for submission, browsing, and download. The PharmGKB is envisioned as an integrated research tool and repository for genetic, genomic, molecular and cellular phenotype data and clinical information on research participants in pharmacogenomics research studies. As of October 9, 2006, the PharmGKB reportedly contained information on 230 genes and its variants and 426 drugs. PharmGKB is comprised of clinical and basic pharmacokinetic and pharmacogenomic research data on, but not limited to, the cardiovascular, pulmonary and cancer pathways, and metabolic and transporter domains [102]. These data are publicly accessible on the internet for research purposes. In the short term, it is conceivable that biomarker data repositories such as PharmGKB will become an important aid to researchers in obtaining clinical proof-of-concept to understand how genetic variation among individuals contributes to differences in reactions to drugs. Looking further, such theragnostic databases may accumulate sufficient 'biomarker–phenotype' correlative studies to be able to inform population-based GAP2

translational research, a pivotal next step in developing theragnostic-guided treatments and health policy (see also section on GAP2).

It is noteworthy that studies aimed at GAP1 knowledge translation can be mistakenly framed as the sole translational research activity on the path from basic biomarker research to individually tailored drug therapy. Although the early phase translational biomarker studies noted above provide preliminary insights into predictive value (e.g., sensitivity/specificity) of theragnostic tests in humans, the complete range of pharmacokinetic and pharmacodynamic variability and attendant predictive performance of theragnostic biomarkers within and among human populations are seldom available at the end of GAP1 translational research. This becomes an acute concern, particularly in the case of theragnostic tests based on genomic, proteomic or other -omic technologies.

An important caveat in pharmacogenomic association studies aimed at personalized medicine is that they exploit the principle of linkage disequilibrium (LD), the co-occurrence of alleles at different genetic loci at a frequency greater or lesser than what would be expected due to random association alone [13,15,16]. Consequently, the genetic loci that are reportedly associated with drug response or toxicity may not necessarily correspond to the causal genetic variants. The degree of LD also varies markedly in different regions of the genome, as well as among different populations [17–19]. Thus, unless the causal genetic variants are ascertained, the informativeness of genetic markers identified in small-scale GAP1 translational research for prediction of drug response will be fraught with uncertainty when therapeutic forecasts are extended more broadly to other populations beyond the immediate study sample [20]. Furthermore, due to the multigenic nature of most human diseases and pharmacological traits, pharmacogenomic biomarkers can be, but are not always, population-specific; divergent sets of genes may influence the clinical phenotypes in different populations [20,21]. Attention to a large range of social and environmental factors (e.g., smoking, diet or other lifestyle factors) and gene–environment interactions will also be essential to appreciate individual, geographic and population variability in drug effects. Hence, these considerations collectively call for much larger scale population-based GAP2 translational theragnostic biomarker research.

GAP2: translation from clinical proof-of-concept to treatment guidelines based on theragnostic tests

For theragnostic tests and the personalized medicines to become a reality at point of patient care, a broader scope and types of human genetic (for example, other than single nucleotide polymorphisms), proteomic and metabolomic variation will need to be explained, well beyond what is achievable in small-scale GAP1 translational research studies. This is significant particularly from a clinical standpoint, as noted above, because the only barrier between a patient and severe toxicity or treatment failure will be the theragnostic test itself. In cases where the diagnostic sensitivity/specificity of the test is not sufficiently robust, a number of ethical and legal issues emerge related to knowledge transfer, regulation of novel technologies, commercialization and professional responsibility [7,22,23].

A case in point on the limits of GAP1 translational research is the CYP2D6 drug-metabolizing enzyme that contributes to disposition of several important psychotropic agents. Within the *CYP2D6* gene itself, certain alleles are typified by polymorphisms (for example, insertions/deletions) other than the traditionally investigated common nucleotide substitutions [24]. Attention to rare genetic variants will also be necessary in cases where the test results inform critical decisions on choice of drug prescription or dosage. The required sensitivity and specificity of molecular genetic assays, in a clinical diagnostic context, must be markedly higher than the technical standards acceptable for purely research purposes or biomarker discovery applications. Furthermore, clinicians who are familiar with the rapid turnaround times and relatively low cost of clinical chemistry tests may understandably demand a comparable ease of access, affordability and rapidity of test result (e.g., within several days or ideally by the end of each patient's visit). With the exception of a few specialized research centers and tertiary care centers in developed countries, these 'diagnostic standards' are simply not achievable or are well beyond the present capacity of public healthcare systems in many countries [8].

Another avenue for GAP2 translational theregnostics research, and one that has thus far been overlooked, is the use of population databases such as UK Biobank, the Estonian Genome Project, the Icelandic Healthcare Database and the proposed Quebec CARTaGENE project [10–12]. Thus far, the primary focus of these population databases has been the identification of

disease susceptibility genes with applications towards drug target discovery or disease risk assessment [25,26]. Conceivably, these biological and phenotypic/epidemiologic repositories can also contribute to the identification and/or validation of theragnostic tests to individualize drug treatment regimens. Potential benefits of population biobanks, and the means or research methodologies to achieve them over the long term, still remain ill-defined. The data contained in biobanks are quite variable in terms of content and quality, as well as the type of consent obtained from participating subjects. There is little harmonization or standardization of data collection and banking procedures amongst biobanks [103], making the exchange and sharing of data practically and financially difficult, a situation further compounded by common professional tendencies in biomedicine and human genetics research towards data withholding [10,27–29]. It would be timely to initiate key stakeholder meetings and wider community consultations to examine the impact of biobanks and theragnostic testing on medical practice, health professionals' education, awareness, professional responsibilities and how best to communicate and translate findings related to new theragnostic markers identified or validated in biobanks.

It is still unclear whether the dual objectives of biomarker validation for disease susceptibility and drug response variation are both achievable within the constraints of a single population biobank. For instance, disease phenotypes can be ascertained dichotomously as 'present' or absent'. In contrast, for drug response phenotypes to be clinically meaningful, they may require a higher resolution definition with continuous measures and repeated observations over time. Drug response may also fluctuate due to drug–drug interactions or time-dependent changes in physiological states (e.g., diurnal rhythms or menstrual cycle). Another more focused application of population biobanks could be the identification of gene–environment interactions in the context of drug therapy. Populations of patients who are tracked for their drug response over long periods of time can help to discover and validate rare but serious drug side effects during postmarketing safety assessments. Consider, for example, the relatively uncommon but lethal cardiac side effects of the selective cyclooxygenase 2 (COX-2) inhibitor rofecoxib (Vioxx®) that could not be detected reliably in small-scale early phase premarketing clinical trials. However, given the global nature of contemporary bioscience research, drug development, and marketing of new medicines, it is very likely that a coordinated multibiobank approach to theragnostic applications will be necessary.

Technical, bioinformatic and phenomic integration in theragnostics: rationale for centralized translational clinical research centers

Success in translational theragnostic research depends on expertise in three fundamental domains:

- Core technical expertise to generate high-throughput biomarker data;
- Collection of large volumes of phenotypic data from patients treated with drugs;
- Ability to perform correlative bioinformatics analyses between biomarker data and drug related phenotypes.

Due to the rapidly declining cost of genotyping and other biomarker genotypic technologies, availability of phenotypic data is now the most crucial and rate limiting step among these three domains [30]. This creates a statistical conundrum: in order to attain adequate statistical power to allow correction for multiple testing and association analyses among multiple biomarkers and clinical end points, researchers require an increasingly larger number of human subjects or biological specimens (for example, tumor biopsy material) to accompany the high-throughput theragnostic biomarker data [29,30]. Therefore, in addition to the technical integration, there is an acute need to establish local, national and international 'phenomic' databases that can integrate drug-related phenotypes across a broad range of treatment outcomes in different therapeutic areas, using both public and privately-sponsored pharmaceutical research and clinical trial data (a significant challenge given the proprietary, and thus secret, nature of such data).

To the extent that integration across technical (for example, amongst genomic–proteomic–metabolomic divides) and phenotypic dimensions is an emerging and timely theme in translational theragnostic research, what are some of the optimal research strategies that can deliver on this goal? We submit that one of the internationally recognized integrated models for translational clinical research is the General Clinical Research Centers (GCRCs), a national US network of approximately 78 centers, mostly located within the research hospitals of academic medical centers. The primary mission

of the GCRCs is to provide a research infrastructure for clinically oriented investigators. Furthermore, GCRCs act as an important link between molecular research and clinical practice, allowing investigators to translate knowledge gained through basic research into the development of new or improved diagnostics and therapeutics for patient care. With the emergence of theragnostics and increasing public demands for personalized medicine, it would be timely to amend the existing GCRC research infrastructure to accommodate integrated biomarker research towards the eventual goal of individually-tailored drug therapy. Conceivably, theragnostic-oriented GCRC networks can also serve to pool phenotypic information derived from industry-sponsored clinical trials (assuming stricter requirements for data disclosure) along with publicly funded academic pharmaceutical research across medical disciplines both at institutional, national and international levels.

Expert commentary & future outlook

Personalized drug therapy is not a new concept [15,16,31]. However, theragnostic testing is beginning to transform medical practice in a fundamental manner by placing a greater emphasis on the notion of probability [7,32], instead of traditional expectations about definitive prediction of treatment outcomes. The scope of research in this field has changed over the past several years with the availability of new technical and methodological approaches such as proteomics and metabolomics. At the moment, these promising technologies are best suited for exploratory research and remain to be validated both in terms of sensitivity/specificity of the data they generate and their mechanistic relevance in explaining variability in treatment outcomes in a population context. In parallel to these new technologies, the precision of existing technologies in applied genomics (i.e., high-throughput genotyping and gene-expression analysis) has increased while the unit cost of assays has markedly decreased.

Arguably, all these technical advances reflect an emerging 'engineering triumph' in biomarker research and more broadly, in diagnostic medicine [33]. However, for this to translate into a 'biological triumph' in a clinically meaningful manner, there is an acute need for the integration of biomarker data. However, our fear is that continued reliance on a singular biomarker technology platform by different stakeholders may result in an artificial compartmentalization (or fragmentation) of biomarker research. For example, human geneticists and pharmacogenomics researchers may favor genotyping and gene expression analyses, while biochemists may primarily utilize proteomic methods. On the other hand, drug effects are determined multifactorially, and the human genome is subject to poorly understood plasticity. Thus an integrated and promiscuous approach to biomarker technology platforms – whether they rely on genomic, proteomic and/or other methodologies – should be adopted so long as it explains individual differences in drug efficacy and safety in a mechanistic and clinically meaningful manner. It is against this need for technical and phenotypic integration that the new subspecialty of theragnostics and the attendant requirement for translational research centers are emerging.

Despite considerable efforts in GAP1 translational biomarker research, there remains a large and serious gap in further translation of biomarker data obtained in FIH pharmacogenomic proof-of-concept studies to a population level for the development of personalized treatment guidelines using genetic or other types of theragnostic tests. Large-scale biobanks are being developed in several countries around the world to meet these objectives. These databases concern the general population as opposed to particular patient groups or families. The amount of information gathered on the individual, as well as the types of diseases studied, constitute a divergence from the genetic registers of the past as well as from the gene-hunting (or discovery) research of today. Another change in the research paradigm is the desire for public consultation. These databases depend on public participation and assent. Therefore, it is important to encourage a free, open and useful dialogue among all stakeholders involved.

Due to the inherent focus on theragnostic 'product development', whether it be in biobanks or GAP1 translational research, there may be cause for concern over how much weight will be given to more fundamental research that may not directly have an application in the clinic [29]. Such concerns coincide with a shift in the perceived mission of academe and medical research, particularly with regards to the applied sciences. In addition to being sites of advanced teaching and research (the university's 'first' and 'second' missions), universities must now engage in knowledge transfer that leads to technology development and economic growth (the 'third mission'), a role that has proven popular with

governments, industries and universities worldwide [1,29]. To facilitate this third mission (and some would argue, to transform universities into 'entrepreneurial' institutions), laws and policies have been implemented to ensure strong protection of intellectual property rights and facilitate commercialization and technology transfer. Such patents can still have serious negative consequences for the conduct of academic research and free sharing of data amongst population biobanks [3,29].

Advances in theragnostics will likely take place in small but significant steps. Development of the necessary research resources – i.e., interdisciplinary research centers, harmonized large-scale biobanks, and so on – to enable the integration of molecular biomarker data with the attendant environmental factors, and the subsequent translation into clinical practice and regulatory frameworks needs to be planned much sooner. There is a clear need for translational clinical research centers that can integrate the full range of biomarker data from different levels of the biology and technology platforms (e.g., genomic, proteomic and metabolomic) as well as a broad range of pharmacological phenotypes (i.e., phenomics) in a way that is meaningful from both the physicians' and patients' individual perspectives.

Highlights

- In the context of theragnostics, translational research is clearly a complex and multistage process.
- Inadequate recognition of two major bottlenecks impedes the translation of current theragnostics research to the point of patient care: translation from basic science to first-in-human proof-of-concept; and translation from clinical proof-of-concept to development of evidence-based personalized treatment guidelines.
- The need to harmonize large-scale population biobanks to enable translation of theragnostics research is fraught with scientific, technical, social and political challenges. However, these challenges are not insurmountable.
- Broad public and stakeholder engagement is essential for the development of effective and socially acceptable biobanks that can allow a deeper understanding of both disease pathophysiology and individual determinants of variability in drug response and toxicity.
- The application of theragnostics at the point of patient care, i.e., the dream of personalized medicines, requires broad scale interdisciplinary collaboration along the development pathway, from rigorous basic and applied -omics research to the ethical implementation and delivery of safe and effective therapeutics.
- There is an acute need for resource development, for example, translational clinical research centers, for integration of biomarker data from different levels of the biology and technology platforms, as well as a broad range of pharmacological phenotypes in a way that is meaningful from both the physicians' and patients' individual perspectives.

Bibliography

1. Williams-Jones B: Knowledge commons or economic engine – what's a university for? *J. Med. Ethics* 31, 249–250 (2005).
2. Cascorbi I: Genetic basis of toxic reactions to drugs and chemicals. *Toxicol. Lett.* 162, 16–28 (2006).
3. Ozdemir V, Williams-Jones B, Glatt SJ *et al.*: Shifting emphasis from pharmacogenomics to theragnostics. *Nat. Biotechnol.* 28, 942–946 (2006).
4. Fourie J, Diasio R: Pharmacogenetics. In: *Cancer chemotherapy and biotherapy: principles and practice, 4th edition.* Chabner BA, Longo DL (Eds), Lippincott Williams and Wilkins Co., Philadelphia, PA, USA, Chapter 24, p529–548 (2005).
5. Kumar S, Mohan A, Guleria R: Biomarkers in cancer screening, research and detection: present and future: a review. *Biomarkers* 11, 385–405 (2006).
6. Nicholson JK, Connelly J, Lindon JC, Holmes E: Metabonomics: a platform for studying drug toxicity and gene function. *Nat. Rev. Drug Discov* 1, 153–161 (2002).
7. Hopkins MM, Ibarreta D, Gaisser S et al.: Putting pharmacogenetics into practice. *Nat. Biotechnol.* 24, 403–410 (2006).
8. Williams-Jones B, Ozdemir V: Pharmacogenomic Promises: Reflections on Semantics, Genohype and Global Justice. In: *Emerging Technologies: From Hindsight to Foresight.* Einsiedel E (Ed.), University of Calgary Press, Calgary, Canada (2006).
9. US Department of Health and Human Services. Food and Drug Administration: Innovation/stagnation. Challenge and opportunity on the critical path to new medical products (March 2004).
10. Godard B, Knoppers BM: Emerging duties in professional disclosure. In: *Genetic Testing: Care, Consent, and Liability.* Sharbe NG, Carter RF (Eds), John Wiley & Sons Inc., Hoboken, NJ, USA (2006).
11. Godard B, Marshall J, Laberge C, Knoppers BM: Strategies for consulting with the community: the cases of four large-scale genetic databases. *Sci. Eng. Ethics* 10, 457–477 (2004).
12. Godard B, Schmidtke J, Cassiman JJ, Ayme S: Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective. *European J. Hum. Genet.* 11(Suppl. 2), S88–S122 (2003).
13. Daly AK: Candidate gene case–control studies. *Pharmacogenomics* 4, 127–139 (2003).
14. Tamaoki M, Gushima H, Tsutani K: Pharmacogenomics in Asia. *Pharmacogenomics* 5, 1023–1027 (2004).
15. Bondy B, Zill P: Molecular methods for individualization of psychotropic drug treatment. *Curr. Pharmacogenomics* 4, 177–189 (2006).
16. Eichelbaum M, Ingelman-Sundberg M, Evans WE: Pharmacogenomics and individualized drug therapy. *Annu. Rev. Med.* 57, 119–37 (2006).

17. Patil N, Berno AJ, Hinds DA *et al.*: Blocks of limited haplotype diversity revealed by high-resolution scanning of human chromosome 21. *Science* 294, 1719–1723 (2001).
18. Goldstein DB, Tate SK, Sisodiya SM: Pharmacogenetics goes genomic. *Nat. Rev. Genet.* 4, 937–947 (2003).
19. Hoehe MR: Haplotypes and the systematic analysis of genetic variation in genes and genomes. *Pharmacogenomics* 4, 547–570 (2003).
20. Suarez-Kurtz G: Pharmacogenomics in admixed populations. *Trends Pharmacol. Sci.* 26, 196–201 (2005).
21. Holtzman NA: Putting the search for genes in perspective. *Int. J. Health Serv.* 31, 445–461 (2001).
22. Williams-Jones B: Be Ready against cancer, now: direct-to-consumer advertising for genetic testing. *New Genet. Soc.* 25, 89–107 (2006).
23. Burgess MM: Beyond consent: Ethical and social Issues in genetic testing. *Nat. Rev. Genet.* 2, 147–152 (2001).
24. Daly AK: Pharmacogenetics of the cytochromes P450. *Curr. Top Med. Chem.* 4, 1733–1744 (2004).
25. Corrigan OP, Williams-Jones B: Pharmacogenetics: the bioethical problem of DNA investment banking. *Stud. Hist. Philos. Biol. Biomed. Sci.* 37, 549–564 (2006).
26. Godard B, Hurlimann T, Letendre M, Egalite N: INHERIT BRCAs. Guidelines for disclosing genetic information to family members: from development to use. *Fam. Cancer* 5, 103–116 (2006).
27. Blumenthal D, Campbell EG, Gokhale M, Yucel R, Clarridge B, Hilgartner S, Holtzman NA: Data withholding in genetics and the other life sciences: prevalences and predictors. *Acad. Med.* 81, 137–145 (2006).
28. Austin MA, Harding S, McElroy C: Genebanks: a comparison of eight proposed international genetic databases. *Community Genet.* 6, 37–45 (2003).
29. Williams-Jones B, Ozdemir V: Enclosing the 'knowledge commons': patenting genes for disease risk and drug response at the university-industry interface. In: *Ethics and Law of Intellectual Property. Current Problems in Politics, Science and Technology.* Lenk C, Hoppe N, Andorno R (Eds). Ashgate Publishing, London, UK, p177–209 (2006).
30. Ozdemir V, Kalow W, Tothfalusi L, Bertilsson L, Endrenyi L, Graham JE: Multigenic control of drug response and regulatory decision-making in pharmacogenomics: The need for an upper-bound estimate of genetic contributions. *Curr. Pharmacogenomics* 3, 53–71 (2005).
31. Preskorn SH: Pharmacogenomics, informatics, and individual drug therapy in psychiatry: past, present and future. *J. Psychopharmacol.* 20(4 Suppl.), 85–94 (2006).
32. Gunes A, Someya T, Fukui N, Sugai T, Williams-Jones B, Ozdemir V: Pacific Rim Association for Clinical Pharmacogenetics – 13th Annual Conference: Pharmacogenetics-Based Individualized Therapy, 28–30 June, Changsha, China (2006).
33. Terwilliger JD, Weiss KM: Confounding, ascertainment bias, and the blind quest for a genetic 'fountain of youth'. *Ann. Med.* 35, 532–544 (2003).

Websites

101. National Institutes of Health Roadmap for Medical Research. http://nihroadmap.nih.gov
102. Pharmacogenetics & Pharmacogenomics Knowledgebase (PharmGKB). www.pharmgkb.org
103. Wellcome Trust: From Biobanks to Biomarkers. Wellcome News 45, December 2005. www.wellcome.ac.uk/doc%5Fwtx032108.html

Asymmetry in Scientific Method and Limits to Cross-Disciplinary Dialogue: Toward a Shared Language and Science Policy in Pharmacogenomics and Human Disease Genetics

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Pharmacogenomics is a hybrid field of experimental science at the intersection of human disease genetics and clinical pharmacology sharing applications of the new genomic technologies. But this hybrid field is not yet stable or fully integrated, nor is science policy in pharmacogenomics fully equipped to resolve the challenges of this emerging hybrid field. The disciplines of human disease genetics and clinical pharmacology contain significant differences in their scientific practices. Whereas clinical pharmacology originates as an experimental science, human disease genetics is primarily observational in nature. The result is a significant asymmetry in scientific method that can differentially impact the degree to which gene-environment interactions are discerned and, by extension, the study sample size required in each discipline. Because the number of subjects enrolled in observational genetic studies of diseases is characteristically viewed as an important criterion of scientific validity and reliability, failure to recognize discipline-specific requirements for sample size may lead to inappropriate dismissal or silencing of meritorious, although smaller-scale, craft-based pharmacogenomic investigations using an experimental study design. Importantly, the recognition that pharmacogenomics is an experimental science creates an avenue for systematic policy response to the ethical imperative to prospectively pursue genetically customized therapies before regulatory approval of pharmaceuticals. To this end, we discuss the critical role of interdisciplinary engagement between medical sciences, policy, and social science. We emphasize the need for development of shared standards across scientific, methodologic, and socioethical epistemologic divides in the hybrid field of pharmacogenomics to best serve the interests of public health.

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Coalescence of Clinical Pharmacology and Human Disease Genetics by Shared Application of New Genomic Technologies

The scope of scientific inquiry in clinical pharmacology and human disease genetics has expanded over the past several years with the development of population-based databases (eg, UK Biobank, the Estonian Genome Project, GenomEUtwin, CARTaGENE) and the introduction of new genomic technologies, such as high-throughput analysis of gene expression.[1–5] These genomic technology platforms aim to characterize multiple genes, often on the order of tens of thousands, to enable an integrated view of genetics and its role for drug efficacy and safety. The origin of the genomic technologies is not, however, rooted in pharmacology but can be traced back to advances made on the heels of the Human Genome Project.[6–8]

Intensive deoxyribonucleic acid (DNA) sequencing efforts in the late 1990s, facilitated by the coalescence of traditional methodologies used in human genetics and cell biology, resulted in technology platforms capable of generating large volumes of data in very short time frames. Genomic technologies are now increasingly adopted in pharmacologic sciences, with an attendant expansion of the scientific process. These advances start with the view that a broader investigation of the multiple components of a complex biologic pathway targeted by a pharmaceutical compound may provide better insights into the mechanisms of drug action and ultimately allow individualization of drug therapy.[9] Hence, clinical pharmacology and human genetics research are rapidly coalescing, in part owing to such broad and shared applications of genomic technologies.

When scientific disciplines meet toward a common goal, both technical expertise and expectations of practitioners for what constitutes scientific merit inevitably struggle for position. The extent of similarities and discrepancies among the views of scientists from the respective disciplines and the ensuing critical debate on new hypotheses or technologies in a given field often serve as catalysts for the rejection or wide adoption of new hypotheses and technologies.[10] Important innovations emerge from creative interdisciplinary sharing of methods and concepts, yet it is essential that precautionary principles are adhered to in standards for scientific validity and reliability.[11–14]

Whereas clinical pharmacology is an experimental science, most genetics research on human diseases uses a scientific approach that is primarily observational. This results in an asymmetry in scientific method that can differentially impact the degree to which environmental components of phenotypic variability are controlled, including the sample size requirements of each discipline. The number of subjects participating in observational genetic studies of diseases is often used as a key criterion of attendant scientific value; it is also a significant driver of which 'disease gene' discovery is worthy of further policy-oriented translational research or application at the point of patient care. Because environmental factors (and the attendant confounding) are difficult to discern or control in observational study designs, there is an expectation, particularly on the part of the policy makers familiar with population health and large-scale epidemiologic studies, of a large sample size (eg, from several hundreds to thousands) in genetic studies on disease predisposition. Yet these requirements do not necessarily apply to experimental study designs.

Environmental confounding can (and we suggest should) be monitored more readily by scientists in experimental sciences (eg, in pharmacology or pharmacogenomics) prior to or during the execution of the study. Failure to discern such discipline-specific nuances for differential environmental confounding in genetic studies rooted in either pharmacology or disease predisposition will bias expectations for sample size requirements, along with perceptions of the merit of new genomic discoveries. Such interdisciplinary differences in norms and expectations regarding scientific merit may lead to inadvertent dismissal of methodologically sound small-scale exploratory pharmacogenomic studies as new policies are being developed for genomics research in population-based databases. Some of these pharmacogenomic studies may well have appropriate statistical power to detect genetic components of pharmacologic variability.

Pharmacogenomics is usually defined as the study of variability in drug response using information from the entire genome of a given individual patient.[1,2,4] Pharmacogenetics, by contrast, is hypothesis driven

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and focuses on a limited set of candidate genes selected based on a priori observations of disease susceptibility, drug absorption, metabolism, transport, and excretion, as well as drug targets, as opposed to a genome-wide hypothesis-free approach in pharmacogenomics. It is noteworthy that pharmacogenetics and pharmacogenomics are also interdependent: once a novel gene(s) of relevance for mechanism of drug action is identified through the genome-wide pharmacogenomics search, such individual genetic biomarkers require further validation and follow-up by pharmacogenetics before they can be routinely applied in clinical medicine. For the purpose of the present discussion, we use the term *pharmacogenomics*, but many of the concepts discussed herein will also be applicable to pharmacogenetic investigations.

The objective of the present comparative analysis is to identify and elaborate on these significant asymmetries between clinical pharmacology and human disease genetics in the hybrid field of clinical pharmacogenomics. We emphasize the importance of recognizing pharmacogenomics as an experimental form of science. This broader view of pharmacogenomics addresses an ethical and science policy imperative to favor prospective clinical pharmacogenomic investigations over the ad hoc retrospective biomarker investigations that have, thus far, typified biomarker applications at the point of patient care or late-stage drug development.

Expectations and Challenges for Policy Making in Interdisciplinary Science

Expectations about the merit or promise of a biotechnology or a new scientific field evolve through a complex and subtle interaction of (1) media interest and consumer demand in the society (eg, patients, caregivers, and physicians) for better therapeutic products and services; (2) dialogue among scientists, governments, and policy makers to ensure that the latest scientific standards are met and empirically grounded interdisciplinary science policies are developed; and (3) corporate or private sector marketing of resulting technologies.

Within the process of policy making, there may be increased complexity (and unpredictable outcomes) when disciplinary boundaries are crossed by individual regulators or scientists investigating the broad application of a novel discovery or technology in multiple fields of scientific inquiry. This situation is particularly evident with the application of genomic, proteomic, or other high-throughput '-omics' technologies in fundamental and applied bioscience research. Such cross-disciplinary journeys are not without their challenges. Scientists regularly encounter stigma and resistance to novel hypotheses or methods, and collaborations can reach an impasse when the norms governing scientific merit in a discipline are not mutually reconciled or renegotiated in light of the particular attributes of each field of inquiry. Thus, while evaluating new technologies and concepts borrowed from diverse but complementary disciplines, regulators engaged in policy making need to employ multiple lenses to discern disciplinary nuances.[15–17] This is a timely consideration for, as noted earlier, many countries and the private sector in applied genomics are in the process of developing large-scale genomic databases and biobanks.[3,18,19] When drawing conclusions on the public health significance of new genetic discoveries and their potential for application in patient care, identification of the particular characteristics of human disease genetics and pharmacogenomics that strengthen or weaken the credibility of the resulting methods or products should be taken into account.

Contrast between Observational and Experimental Study Designs: Why Is This Relevant to Interdisciplinary Policy Development for Pharmacogenomics?

Since the late 1990s, the idea of exploring pharmacologic phenotypes (eg, drug effectiveness and side effects) as another promising dimension of genetic research has attracted a number of human geneticists to the field of clinical pharmacology and vice versa. This bidirectional exchange of scientific expertise benefited and complemented the classic pharmacologic approaches to questions of variability in pharmacokinetics and pharmacodynamics. At the same time, there has been a tendency to view pharmacologic responses akin to disease phenotypes. There are, however, several fundamental differences between human disease genetics research and clinical pharmacogenomics that require particular attention for a balanced interpretation of scientific merit in genetic studies of pharmacologic phenotypes (Table 1).

A fundamental goal of human genetics research is to establish the causal links between genes and disease phenotypes or characteristics. Yet most common complex human diseases initiate and progress over a considerable period of time before clinical signs and symptoms manifest. This means that environmental contributions to disease phenotypes are difficult to determine without longitudinal studies. It can be prohibitively expensive to discern disease-environment interactions when long-term observation and follow-

Table 1 Distinctions in Scientific Method (Experimental vss Observational) between the Disciplines of Clinical Pharmacogenomics and Human Genetics, Respectively, that May Differentially Influence the Sample Size Requirements and the Attendant Perceptions on Scientific Merit

Discipline-Specific Attribute	*Clinical Pharmacogenomics*	*Genetics of Common Complex Human Diseases*
Study design considerations		
Most common design	Experimental; the investigator can actively manipulate the drug dose or exposure	Observational; the investigator does not induce the disease and instead quantifies phenotypes, usually after disease is clinically manifested
Within-subject study design	Feasible	Not feasible or can be unethical
Reduction of bias in study design with use of randomization	Feasible	Not feasible; disease susceptibility is not subject to assignment and, rather, is observed
Phenotype considerations*		
Temporal attributes of phenotype	Both prospective and retrospective samplings are feasible	Often retrospective sampling of disease phenotypes is required or the only feasible option
Repeated measures data collection to enrich phenotypic characterization	Feasible	In most cases, it can be prohibitively expensive owing to long time frames required for clinical manifestation of disease signs and symptoms
Environmental contribution to phenotypes	Calculable	Often incalculable; difficult to control or eliminate when calculable
Baseline phenotypes	Discernible prior to drug administration; this allows unequivocal calculation of the net drug-related phenotypes by subtracting the predrug phenotypes from the composite phenotypes obtained post–drug administration	Often not discernible owing to slow initiation and progression of most common complex human diseases over many years
Rechallenge/challenge with independent variable (ie, drug treatment or disease induction or susceptibility)	Phenotype ascertainment and its 'drug-relatedness' can be further strengthened by discontinuation of drug treatment followed by subsequent rechallenge with drug treatment	Disease processes often cannot be experimentally switched 'on' or 'off' to ascertain the attendant clinical phenotypes
Other distinctions		
Feasibility of in vitro studies to estimate the scope of allelic or locus genetic heterogeneity	Drug itself can be used as a 'probe' by virtue of its physicochemical interactions with drug-metabolizing enzymes, transporters, or molecular targets for efficacy to discern the high-priority candidate pharmacokinetic and pharmacodynamic pathways and the attendant locus and allelic genetic heterogeneity In vitro studies are feasible to estimate the upper-bound limit on the number of plausible candidate genes, particularly in the case of pharmacokinetic pathways or molecular drug targets	Often no biologic or physicochemical probe is available to empirically discern the type or the number of disease-related biologic pathways (with the exception of certain environmentally induced cancers or diseases)

*Our comparative analyses should not suggest that clinical pharmacogenomics, as a discipline, is uniformly at a greater advantage in achieving optimal phenotype ascertainment and study design than human disease genetics research. Instead, the distinctions highlighted are context specific and emanate primarily from the differences in the scientific method between the two disciplines (experimental vs observational, respectively). Moreover, phenotypic ascertainment of certain pharmacologic phenotypes, particularly in the case of categorical treatment outcomes (eg, responders and nonresponders), can meet with discordance among physicians, whereas the availability of disease diagnostic criteria (eg, *International Classification of Diseases*) may facilitate uniformity in phenotype ascertainment in human disease genetics research.

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up are required in ostensibly healthy individuals who are predicted to develop a disease phenotype in the far too distant future. By contrast, as an experimental science, clinical pharmacology is able to elicit phenotypes (in a controlled laboratory or hospital setting) within a matter of a few minutes (eg, antihypertensive drugs), days, or weeks (eg, anticancer medications), during which it is feasible to measure and account (to a certain extent) for environmental components of pharmacologic variability. Seen in this light, it is possible to understand drug effects as an acquired form of biologic variance.[20]

The measurability of drug effects and the recognition that drugs are well-characterized modifiers of normal life processes or (patho)physiologic events led, nearly 50 years ago, to establishment of the origins of pharmacogenomics as a new medical subspecialty.[1,2,9] The technical advances over the past decade have, in effect, blurred the interdisciplinary boundaries in pharmacogenomics research. For example, even though the observational and experimental nature of human disease genetics and pharmacogenomics, respectively, may allow different degrees of control over environmental influences, such disciplinary nuances are not always recognized. This recognition is important since sample size requirements to achieve an optimal signal to noise ratio for discovery of genetic markers of pharmacologic phenotypes and disease-related traits can markedly differ.

It should be stressed that reproducibility of new genetic findings in independent samples is required in both human disease genetics research and pharmacogenomics, in part owing to population-to-population differences in the type and frequency of genetic susceptibility loci for a given phenotype in the human genome. In addition, large sample sizes are often required to detect the small individual effects of numerous genes and their complex gene-gene/gene-environment interactions on drug response or disease phenotypes. We suggest, however, that a smaller sample size is sufficient for such replication studies in clinical pharmacogenomics owing to greater control of environmental confounding in pharmacologic phenotypes.

In the late nineteenth century, Paul Ehrlich proposed the presence of "chemoreceptors" on microorganisms and cancer cells that differ from the host organism—a precursor to the current concept of molecular drug targets and selective toxicity of modern medicines.[21] The presence of discernible targets suggests that drugs can serve as invaluable probes to guide the identification of plausible pharmacokinetic or pharmacodynamic biologic pathways. One concrete example is in vitro drug metabolism studies that reliably identify the CYP-450 enzymes that may contribute to clinical pharmacokinetics of a new therapeutic candidate. Because only a handful of CYP-450 enzymes are responsible for drug metabolism, these in vitro approaches can provide a practical upper-bound limit on the number of candidate genetic loci and, by extension, the scope of genetic heterogeneity causally related to variability in a clinical pharmacology phenotype.[17,22]

These theoretical and applied nuances collectively underscore the fact that environmental factors and genetic heterogeneity can be discerned or controlled more readily (although never totally controlled) in clinical pharmacogenomics than human genetics by virtue of pharmacology's nature as an experimental science (see Table 1).[23] Hence, for a given sample size, our ability to detect genetic markers may be significantly enhanced by careful consideration and accounting for environmental effects through experimental study designs in pharmacogenomics. Additionally, the application of randomized and prospective pharmacogenomic studies is an entirely feasible strategy through which confounding by environmental factors can be further reduced.

A rational strategy is needed to assign priority to drugs that are subject to a higher degree of genetic regulation.[22] This would enhance the signal to noise ratio for genetic factors and could permit pharmacogenomic association studies in smaller number of subjects. Typically, heritability estimates are obtained using the twin method. Twin studies are very useful to establish the genetic components for common complex disease phenotypes (eg, breast cancer) but have limited applicability in pharmacologic responses to drugs. Some of these limitations include difficulties in recruitment of twins and obtaining clinical outcome data in both twins (since the twin pairs may not suffer from the same disease at the same time), as well as the financial cost of twin investigations. To remedy the difficulties associated with the twin approach, a repeated drug administration (RDA) method was proposed by Werner Kalow wherein between- and within-subject variances in drug efficacy or safety are compared.[22,24,25] The RDA method requires the following considerations. In a given individual, within-subject variance (SD_w^2) is determined by environmental factors and measurement errors ($SD_w^2 = SD_{environment}^2 + SD_{measurement\ error}^2$). Notably, the second term ($SD_{measurement\ error}^2$) includes not only measurement error but also biologic variation, random and nonrandom (eg, circadian). On the other hand, between-subject variance (SD_b^2) can be formulated as

($SD_b^2 = SD_{environment}^2 + SD_{genetic}^2 + SD_{measurement\ error}^2$). As originally proposed by Kalow and colleagues,[24] the genetic component (r_{GC}) of variability in a time-dependent pharmacokinetic or pharmacodynamic occurrence can be estimated with the following equation:

$$r_{GC} = \text{Genetic component} = \left(SD_b^2 - SD_w^2\right)/SD_b^2$$

The r_{GC} values approach 1.0 point to overwhelming genetic control, whereas those close to zero suggest that environmental factors dominate. In essence, any dynamic biologic process exhibiting time-dependent decay and negligible carryover effects between repeat observations can be amenable to RDA studies to dissect the genetic contribution to interindividual variability in the corresponding biologic phenotype.[22] Recent applications of the RDA method demonstrate that genetics plays a paramount role in pharmacologic traits hitherto not subjected to pharmacogenomic analysis, such as renal drug disposition and pharmacokinetic variability of the antiretroviral drug didanosine.[26,27]

In our focused comparison of clinical pharmacogenomics and human disease genetics research, it should be clear that despite the application of prospective design, clinical pharmacogenomics cannot completely account for the diverse socioeconomic and environmental factors (eg, other medications, alcohol, diet, workplace, etc.) that will actually affect the patient and potentially result in adverse drug reactions in their day-to-day use of the medication.[28] Moreover, phenotypic measurement of drug effects remains particularly problematic in fields such as psychopharmacology, even in the presence of strict monitoring of environmental effects. The temporal and geographic plasticity of human behaviors (independent from drug treatment) and limitations of clinical rating scales to capture nuanced changes in behavioral responses to drugs introduce uncertainty in ascertainment of pharmacologic phenotypes in psychiatric pharmacogenomics.

Increased Ability to Generate High-Throughput Genomic Data Creates New Sociotechnical Actors and Control Points in the Scientific Process

High-throughput genomic technologies can generate large volumes of genetic data, but they also create a particular statistical conundrum. To attain adequate statistical power and to allow association analysis between multiple genetic factors and clinical phenotypes, researchers require an increasingly larger number of human subjects or biologic specimens (eg, biopsy material from cancerous tissue) to match the high-throughput data generated by new genomic technologies. At first glance, this may come across solely as a logistical issue concerning subject recruitment for clinical pharmacogenomic investigations. Indeed, subject recruitment is, and has always been, an important barrier to successful execution of clinical investigations, whether they are in the area of human disease genetics or pharmaceutical research. However, present throughput of the data generated by genomic methods is vastly greater, by at least several orders of magnitude, compared with only a decade ago.

Reflecting on the three key components of scientific process, from (1) conception of new ideas or study design and (2) execution of a study protocol (eg, including subject recruitment) to (3) analysis and interpretation of new findings, it becomes evident that subject recruitment or collection of clinical phenotypic data is increasingly the de facto critical rate-limiting step or bottleneck in pharmacogenomics.[29,30] The cost of genotyping or other genomic methods has declined markedly, and sophisticated but affordable bioinformatics software and trained personnel are available for association analysis to establish the link between genomic data and clinical phenotypes. This, then, invariably affects the nature of stakeholders and the attendant sociotechnical networks.[29] The role of scientists as gatekeepers in genomic science is being fundamentally altered.[29] In particular, those scientists with small-scale innovative laboratories with limited subject recruitment infrastructure are particularly vulnerable to this new type of large-scale recruitment-driven genomic science. New sociotechnical actors and research coordinators who are not necessarily grounded in human genetics, pharmacology, or social sciences may thus become influential in subject recruitment and, by extension, in research governance.[29,30]

Returning to genomics and science policy, it is noteworthy that the present emphasis on large study sample sizes in clinical pharmacogenomics in part reflects the expectations carried over from observational genetic studies on disease susceptibility as the two disciplines coalesce around shared genomic technologies. If the experimental nature of clinical pharmacogenomic inquiries and the attendant ability to better control or eliminate environmental contributions are not fully appreciated, there will be a risk of premature dismissal of small sample–sized pharmacogenomic studies, even though, as noted earlier, they may have adequate statistical power. Thus, the differences in scientific method in clinical pharmacogenomics and human disease genetics present challenges to practitioners in both research fields. There are

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