



Ethical considerations on pharmacogenomics

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Abstract

Pharmacogenetics offers the prospect of an era of safer and more effective drugs, as well as more individualized use of drug therapies. The effect of human genetic variance on responses to therapy will influence drug-development clinical trials and the use of products in clinical practice. It also promises to raise new ethical challenges, in particular in the fields of research and therapy. Last but not least, pharmacogenetics is likely to fulfil the old dream of an individualised medicine, but in a totally unexpected way.

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1. Introduction

We are rapidly advancing towards the post-genomic era in which genetic information will be part of our everyday life. With the anatomy of the human genome at hand, the whole of society is facing a new challenge. We are increasingly able to interfere with or diagnose diseases, detect genes for monogenic disorders pre-symptomatically, uncover genetic predisposition to common disorders (including cancer and psychiatric disorders), anticipate normal phenotypic traits, and, in the near future will even be able to foresee behavioural traits, such as novelty-seeking behaviour, anti-social behaviour or sexual orientation. The main paradigm shifts provoked by the genomic era in biomedical research have been recently synthesized by Peltonen and McKusick. This genetic and biological revolution will undoubtedly also change clinical trials and clinical practice in the future. Genomics is likely to provide the opportunity to design and develop new drugs. Most pharmaceutical companies expect that the most future drug developments will come from the field of genomics. Along with the design of new drugs, genomics also will provide opportunities to predict responsiveness to drug interventions, since variations in these responses are often attributable to the genetic endowment of the individual. Examples have been identified where common variants in genes involved in drug metabolism or drug action are associated with the likelihood of a good or bad response.

The expectation is that such correlations will be found for many drugs over the next 10 years, including agents that are already on the market. In the long term, it promises to individualise prescription practices by narrowing the target populations exclusively to those for which the medication is safe and effective. The terms ‘pharmacogenetics’ and ‘pharmacogenomics’ (which can be considered to be almost synonymous) reflect this merging of pharmacology and genetics.

Any advancement in terms of knowledge also implies greater levels of complexity and an increasing number of problems; many ethical issues arise in the research and clinical application of pharmacogenetics. In a recent review of the ethical implications of pharmacogenomics, Buchanan at al. pointed out six ethical issues: (1) regulatory oversight, (2) confidentiality and privacy, (3) informed consent, (4) availability of drugs, (5) access, and (6) clinicians’ changing responsibilities [1]. In March 2001, an expert group convened in the International School of Pharmacology of Erice (Italy) issued the “Dichiarazione di Erice sui principi etici della ricerca farmacogenetica” (Erice Declaration of the Ethical Principles of Pharmacogenetics Research). Following that initiatives, in November 2001, the Italian Society of Hospital Pharmacy (Società Italiana di Farmacia Ospedaliera—SIFO) published a proposal of guidelines for the ethical review of clinical trials in pharmacogenetics. SIFO’s guidelines mainly focus on data collection and storage (<http://www.sibce.it/documenti/pdf/lineguida.html>). The document addresses the issues of confidentiality, consent, anonymity and subject protection. An important chapter is also devoted to risks of stigmatisation and commercial

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86 exploitation. In 2002 in the UK, the Nuffield Council on
87 Bioethics established a Working Party, chaired by historian
88 of science Peter Lipton, for the consideration of ethical,
89 legal and social issues raised by the development of phar-
90 macogenetics. The Working Party aims to study ethical
91 issues in the following areas: (a) consent, privacy and con-
92 fidentiality; (b) the management of information about the
93 likelihood of response to treatment; (c) the implications of
94 differentiating individuals into groups based on the likeli-
95 hood of response to treatment. In December 2002, the NCB
96 published a consultation paper currently available on the
97 Internet ([http://www.nuffieldbioethics.org/filelibrary/pdf/](http://www.nuffieldbioethics.org/filelibrary/pdf/pharmacog_consultation.pdf)
98 [pharmacog_consultation.pdf](http://www.nuffieldbioethics.org/filelibrary/pdf/pharmacog_consultation.pdf)); the final report is expected
99 by the end of 2003.

100 In this paper, we shall consider the ethics of pharmaco-
101 genomics from three main perspectives: (1) research; (2) ther-
102 apy; and (3) international justice. We shall conclude with
103 some considerations on so-called “designer” or “tailored”
104 medicine.

105 2. Research

106 Genomic knowledge is assisting drug discovery in several
107 ways: (1) by identifying new targets for traditional drugs;
108 (2) by helping us understand why certain drugs work for
109 some people but not for others; (3) by helping explain drug
110 side-effects; and (4) by allowing the introduction of new
111 classes of drug, such as therapeutic proteins. More than one
112 hundred protein-based drugs are now at advanced clinical
113 trials stages and many more are being developed in labora-
114 tories [2].

115 Several positive ethical implications are expected from
116 the application of pharmacogenetics to the process of de-
117 velopment and discovery of new medicines. First of all, hu-
118 man subjects enrolled in clinical trials are likely to be more
119 protected thanks to pharmacogenetics. An important ethical
120 tenet in medical research involving human subjects is to min-
121 imize risks for participants by optimising the risks/benefits
122 ratio for each participant. The European Convention on Hu-
123 man Rights and Biomedicine states that “Research on a per-
124 son may only be undertaken if all the following conditions
125 are met: (i) there is no alternative of comparable effective-
126 ness to research on humans, (ii) the risks which may be in-
127 curred by that person are not disproportionate to the poten-
128 tial benefits of the research [...]” (art. 16). The application
129 of pharmacogenetic analysis could refine selection criteria
130 allowing to exclude from the study those who are at risk of
131 developing adverse reactions. In particular, people who are
132 at risk of developing side-effects could be excluded from
133 phase I and II studies. During these preliminary phases, the
134 risk of clinical trials will be reduced by targeting people to be
135 investigated according to their genetic make up. In addition,
136 more homogeneous groups of people could be enrolled in
137 phase III, therefore allowing to reduce the numbers of peo-
138 ple involved in studies. Indeed, another important positive

139 consequence, from the ethical point of view, of the appli-
140 cation of pharmacogenomics in medical research concerns
141 the possibility of reducing the number of people enrolled
142 in phase III studies. By identifying people who would not
143 respond on the basis of genetic variation, researchers could
144 improve the design of clinical trials by testing drugs only
145 on people who would be likely to respond, thus conducting
146 smaller but more effective trials. The drug approval process
147 should be facilitated as trials are targeted for specific ge-
148 netic population groups—providing greater degrees of suc-
149 cess. Effectiveness is not only a scientific requirement of
150 any clinical trial but is also an ethical pre-requisite of any
151 research involving human subjects.

152 However, some controversial issues still need to be ad-
153 dressed, the regulation of pharmacogenomics probably
154 being the most important of these. To date, no regulatory
155 authority has specifically addressed the management of
156 pharmacogenetic tests in the research, development and
157 licensing of medicines [3]. Biomedical research involving
158 DNA banking is governed by numerous legal and ethical
159 guidelines, while we lack specific regulations on genet-
160 ics research in clinical drug trials. The need to establish
161 clear procedures for generating and handling genetic in-
162 formation in the context of pharmacogenetic research has
163 led to a cross-industry group proposing standard defini-
164 tions under which such research can be carried out. In-
165 deed, ethics committees and regulatory authorities could
166 find the current diversity of terminologies and approaches
167 quite confusing. In 2000, the European Agency for the
168 Evaluation of Medicinal Products (EMA) set up a work-
169 ing party with the aim of harmonising genetic terms re-
170 quired for pharmacogenetics trial protocols and guidelines
171 (www.emea.eu.int/pdfs/human/regaffair/148300en.pdf). In
172 2001, the US National Institute of General Medicine as-
173 signed a similar task to the Pharmacogenetics Research
174 Network.

175 Tests are another important issue in research. To develop
176 a drug that is effective for a particular sub-group of patients,
177 genetic tests will be necessary for the identification of a
178 specific population, but it is not clear at all whether these
179 tests should become a regulatory requirement in the future.
180 If this is to be the case, pharmaceutical companies will be
181 expected to store an enormous amount of genetic informa-
182 tion for the purpose of pharmacogenetic analysis. Genetic
183 testing involves very sensitive and intimate items of infor-
184 mation. Unlike most general medical information, it pos-
185 sesses an individual, a familial and a collective dimension.
186 Even if genetic material is, by nature, specific and unique
187 to each individual, it can also reveal personal information
188 about blood relatives and indicate some medical trends en-
189 countered in a particular population. The integration of phar-
190 macogenomics into drug development adds new dimensions
191 to the process. The fact that genetic data are manipulated,
192 analysed and stored in this context, calls for the adaptation
193 of legal and ethical standards. We need to address the issue
194 of the level of anonymity that should be accorded to this ge-

195 netic information. We also need to decide whether pharma-
196 ceutical companies which collect samples in the course of
197 research in pharmacogenetics may ask for a generic consent
198 from the donor or whether donor consent should be restricted
199 to specific usage. Finally, we need to establish whether re-
200 searchers should provide individual feedback about genetic
201 information obtained from participants in research in phar-
202 macogenetics.

203 Last but not least, we should address the issue of commer-
204 cial exploitation and intellectual property of pharmaco-
205 genomics databanks. The European Group on Ethics addressed
206 the general issue in its advice number 11 of 21 July 1998 on
207 “Ethical Aspects of Human Tissue Banking”. In point 2.8,
208 the IGE states: “In principle, tissue bank activities should
209 be reserved to public health institutions or non-profit mak-
210 ing organisations. [...] Nevertheless given the current state
211 of development of the sector, it is difficult to exclude tis-
212 sue banking activities by commercial organisations, such as
213 large private laboratories”. In the case of pharmacogenetics,
214 data will be stored in private labs and used for commercial
215 reasons. In the context of clinical trials, it would seem wise
216 to subsequently destroy genetic samples taken specifically
217 for a pharmacogenetic test. However, one cannot exclude the
218 use of modern communication tools, such as the Internet,
219 to allow patients to provide samples for future research yet
220 retain control over them in the light of future developments.
221 Some possible approaches currently being considered in-
222 clude having DNA samples and patient contact details held
223 by an independent third party, who can then release DNA
224 for research after contacting patients using email or the In-
225 ternet [4].

226 In conclusion, it would be advisable for all the guaran-
227 tees currently in place for biomedical research (clinical trials
228 and genetic research) to also be adopted in pharmacogenet-
229 ics research. However, the most relevant ethical implication
230 of pharmacogenetics on research is likely to concern the
231 way in which clinical trials are designed and conducted. A
232 larger number of patients will probably be enrolled in phase
233 I and II studies in order to find the markers of polymor-
234 phism that can predict responses, while a smaller number
235 of patients will be investigated in phase III. Ethics commit-
236 tees and institutional review boards should take into account
237 these changes in order to correctly evaluate research proto-
238 cols. Another emerging issue is genetic tests for detecting
239 those people who are at risk of developing adverse reactions
240 to tested drugs. One day it may be considered unethical not
241 to carry out such tests routinely in clinical trials to avoid
242 exposing individuals to drugs that could be harmful to them.

243 3. Therapy

244 The promise of pharmacogenomics in reconfiguring ap-
245 proaches to drug use has considerable currency. Pharma-
246 cogenomics is expected to improve, even to overturn, current
247 approaches to drug treatment by reducing adverse reactions,

248 increasing drug efficacy and refining prescribing practices. 248
249 Pharmacogenomics is already being used in therapy. For ex- 249
250 ample, a test for common variants of the gene for thiopurine 250
251 methyl transferase—an enzyme that affects the metabolism 251
252 of two antitubercular drugs, azathioprine and mercaptopurine— 252
253 is coming into use for the determination of the right dosage 253
254 of these two medications in acute lymphoblastic childhood 254
255 leukaemia [5]. In Alzheimer’s disease, genetic variations in 255
256 apolipoprotein E not only predict the onset of the disease, 256
257 but also give clues towards the right treatment to slow down 257
258 its progress. The drug tacrine seems to slow the disease’s 258
259 progress in patients who do not have two copies of the gene 259
260 for apolipoprotein E4. Other drugs may benefit patients with 260
261 Alzheimer’s disease who have different gene profiles for 261
262 apolipoprotein E4 [6]. Indeed drugs are designed and pre- 262
263 scribed on a population basis, but each patient is an individ- 263
264 ual. Current therapies are based on a trial-and-error method 264
265 of matching patients with the right drugs and right dosage. In 265
266 the future—at least in the rosy scenario described by many 266
267 scientists—doctors will be able to analyse a patient’s genetic 267
268 profile, define his/her appropriate patient group for a partic- 268
269 ular medicine and prescribe the best available drug therapy 269
270 from the beginning. Current methods of basing dosages on 270
271 weight and age will be replaced with dosages based on a 271
272 person’s genetics. This will maximize the therapy’s value 272
273 and decrease the likelihood of overdose. However, it is dif- 273
274 ficult to ascertain to what extent the enthusiasm of scientists 274
275 towards discovery—and sometimes their direct involvement 275
276 with pharmaceutical companies—may affect their forecasts. 276
277 Perhaps in the future we may all carry a “gene chip assay 277
278 report” that contains our unique genetic profile that would be 278
279 consulted before drugs are prescribed, but at present chips 279
280 allowing the genetic profiling of patients are still science fic- 280
281 tion. There are few doubts that genetic information will be 281
282 able to identify those who cannot take a particular drug, yet 282
283 we are far still far from developing technologies such as a 283
284 genetic cards or similar devices. At present, what we can rea- 284
285 sonably forecast is that tests will become available for deter- 285
286 mining which patients will benefit and which will be harmed 286
287 by certain drugs. This will in any case comprise an impor- 287
288 tant breakthrough; knowing whether a patient will respond 288
289 is important so that the best treatment can be given straight 289
290 away and because of the high cost of some treatments. Dis- 290
291 covering variations in responses is particularly important in 291
292 drugs for psychiatric conditions such as schizophrenia and 292
293 depression and other chronic or recurrent diseases. Major 293
294 cost savings could come from testing for genetic variations. 294
295 Ultimately economic issues will drive pharmacogenomics 295
296 into conventional practice: the cost of drug failures—drugs 296
297 given to people that don’t work, that delay proper treatment, 297
298 that increase the cost of care, the expense of treatments for 298
299 toxicity and the expense of return visits. Adverse drug reac- 299
300 tions occur in a substantial proportion of patients: accord- 300
301 ing to a recent study, about two million Americans are hos- 301
302 pitalised each year because of drug interactions, and about 302
303 106,000 die [7]. Until recently, the only way to identify a pa-

304 tient with a genetic risk factor for a particular adverse drug
 305 reaction was to carry out tedious procedures involving the
 306 administration of a specific marker drug or test substance.
 307 Modern DNA-based tests require only a small sample of tis-
 308 sue blood from a finger prick, cells from a mouth wash or
 309 hair follicle cells. All these elements present several posi-
 310 tive ethical implications. The use of genetic technologies to
 311 reduce the uncertainty surrounding health status and health
 312 risks will increase individual's autonomy. Citizens will be
 313 empowered by having the information they need when they
 314 need it to manage their own risk. Similarly, the application
 315 of pharmacogenomics in planning medical treatment will al-
 316 low to maximise benefits and minimise risks, thus respect-
 317 ing the ethical tenets of beneficence and non-maleficence.
 318 At a time when harmful drug reactions are thought to rank
 319 just after strokes as a leading cause of death in the US, the
 320 potential benefits of tailoring drugs to a patient's genetic
 321 makeup should not be underestimated even from an ethical
 322 point of view.

323 Yet, in spite of this positive scenario, some hurdles re-
 324 main. First of all, some scientific questions need to be asked
 325 about the effectiveness of the application of pharmacogenet-
 326 ics in therapy. The clinical applicability of pharmacogenetic
 327 testing depends on the relative importance of each polymor-
 328 phism in determining therapeutic outcome. As well as hav-
 329 ing genetic variations, individuals are in different states of
 330 health, eat different diets, take different drugs—all of which
 331 may affect responses to drugs. Doctors need to be aware of
 332 whether a drug they are prescribing is subject to pharmaco-
 333 genetic variability without taking it for granted that genet-
 334 ics play the main role in determining a patient's response
 335 to treatment. A general warning in this respect appeared in
 336 the very issue of *Science* which announced the sequencing
 337 of the human genome: "The successes of medical genetics
 338 and genomics during the last decade have resulted in a sharp
 339 shift toward an almost completely genetic view of ourselves.
 340 I find it striking that 10 years ago, a geneticist had to de-
 341 fend the idea that not only the environment but also genes
 342 shape human development. Today, one feels compelled to
 343 stress that there is a large environmental component to com-
 344 mon diseases, behaviour, and personality traits! There is an
 345 insidious tendency to look to our genes for most aspects of
 346 our "humanness", and to forget that the genome is but an
 347 internal scaffold for our existence" [8].

348 The therapeutic applications of pharmacogenomics may
 349 also raise some ethical questions. One fact which may have
 350 ethical implications is that many genetic variants cluster in
 351 racial groups. As a result, it is inevitable that some fairly
 352 small racial populations have genetic variants that make
 353 them particularly vulnerable to some drugs. This can cre-
 354 ate stigmatisation and discrimination and, in some cases,
 355 drug manufacturers may not find it economical to develop
 356 a new drug to aid a potentially small market. The risk of
 357 creating inequities when developing drugs to avert problems
 358 caused by natural genetic differences linked to race is an im-
 359 portant one. Fragmentation of the market into smaller and

360 smaller groups may not justify research and development
 361 expenditures on what would become orphan drugs. In Eu-
 362 rope and in the USA, the 'orphan medicine' status is granted
 363 if there are fewer than 200,000 potential patients. The "or-
 364 phan medicine" status implies various legal and financial
 365 incentives to promote research and drug development. Ob-
 366 viously existing regulations are not based on pharmacoge-
 367 nomics: one may wonder what will happen when pharmaco-
 368 genetic analysis creates hundreds of new "orphan" diseases
 369 and medicines. There is a risk that this new situation might
 370 create a new group of diseases and patients who will be told
 371 by doctors that a drug cannot be administered in their cases.
 372 We need new regulatory measures to encourage the devel-
 373 opment of clinically desirable but economically unprofitable
 374 medicines, otherwise the application of pharmacogenetics
 375 might exacerbate inequalities in the provision of healthcare.

376 Genetic equity does not only concern potential new
 377 "orphan" medicines, but also the obligation to treat those
 378 who have different genetic makeups. For instance, VaxGen
 379 has recently announced that a genetically-engineered AIDS
 380 vaccine, which has been undergoing phase III trials for the
 381 past three years, has failed to show a significant reduction in
 382 the development of HIV among the those who were vacci-
 383 nated. However, the vaccine has indeed shown a significant
 384 success rate, but only in certain ethnic groups, indicating
 385 that black and Asian volunteers may have produced higher
 386 levels of antibodies against HIV than white and Hispanic
 387 volunteers. The vaccine is thus of some interest for certain
 388 ethnic groups, even if they are different from the groups
 389 targeted by the study.

4. International justice and pharmacogenomics 390

391 The genomics revolution will bring about new cures, new
 392 screening devices, and new ways to address medical prob-
 393 lems. Yet the application of the new genetics will come
 394 with a high price tag, at least in the short term. Even in
 395 rich, developed countries, unless steps are taken to prevent
 396 it, we may see a repetition of the "Digital Divide", as ge-
 397 netic technologies become available first to the wealthy or
 398 well-insured. Whether the great human achievement of un-
 399 locking and continuing to understand the secrets of the hu-
 400 man genome turns out in the short term to be a great step
 401 forward for humanity or a luxury for the wealthiest of the
 402 planet depends on the social choices we make in the next
 403 few years. If efforts are not made to spread the benefits to
 404 those most in need of them, then this great achievement will
 405 not truly be realized for many years to come. This holds true
 406 even for pharmacogenetics. Biomedical research is increas-
 407 ingly becoming a collaborative venture between researchers
 408 in different countries with different levels of wealth. The re-
 409 sults of research done in one country will be utilised to seek
 410 regulatory approval in another country. There is therefore
 411 an urgent need for a harmonisation of international guide-
 412 lines and rules governing biomedical research also relating

413 to pharmacogenetics. The first ethical tenet should be to ap-
 414 ply to pharmacogenetic research the current guidelines that
 415 rule the ethics of international clinical trials. In particular,
 416 it seems important to consider the CIOMS' "International
 417 Ethical Guidelines for Biomedical Research Involving Hu-
 418 man Subjects" (revised August 2002). In Guideline 1 (Ethi-
 419 cal justification and scientific validity of biomedical research
 420 involving human beings) it is stated: "The ethical justifi-
 421 cation of biomedical research involving human subjects is
 422 the prospect of discovering new ways of benefiting people's
 423 health. Such research can be ethically justifiable only if it
 424 is carried out in ways that respect and protect, and are fair
 425 to, the subjects of that research and are morally acceptable
 426 within the communities in which the research is carried out.
 427 Moreover, because scientifically invalid research is unethi-
 428 cal in that it exposes research subjects to risks without pos-
 429 sible benefit, investigators and sponsors must ensure that
 430 proposed studies involving human subjects conform to gen-
 431 erally accepted scientific principles and are based on ade-
 432 quate knowledge of the pertinent scientific literature". This
 433 means that pharmacogenomics analysis is ethically accept-
 434 able only if the drugs which have been developed for admin-
 435 istration in conjunction with a pharmacogenetic test are also
 436 distributed to host countries in which testing facilities are not
 437 available.

438 5. Personalised medicine?

439 In the long run, the development of pharmacogenetics will
 440 provide a mechanism to move prescription away from its
 441 current empiricism towards a more "individualised" kind of
 442 drug treatment. There are two sides to this coin; while on the
 443 one hand, the use of pharmacogenomics analysis can have a
 444 positive impact on drug discovery and therapy, on the other
 445 it also entails the risk of promoting "cosmetic medicine".
 446 In the media debate the phrase "cosmetic medicine" evokes
 447 the concept of consumer satisfaction, and acts at the bor-
 448 derline of the realm of health, in areas such as the use of
 449 medication for improving social and working skills, physical
 450 appearance, etc. For instance, many sports scientists warn
 451 that current performance-enhancing drugs may be a thing of
 452 the past once pharmacogenomics are introduced. We live in
 453 a world where people are always seeking to improve their
 454 performances (working, social, athletic, intellectual, sexual,
 455 etc.) as much as possible. Drugs offer a simple, technical,
 456 solution to do the job. Genetic enhancement is not only a
 457 science fiction dream, it is also an important drive of current
 458 research. It has also been said that we live in an addicted
 society, at least in the sense of a society where biochem-

icals are used to find easy solutions to societal problems. 459
 With drugs tailored reliably to an individual's genome and 460
 biochemical symptoms, many of the skills that doctors now 461
 deploy will have become automated. This will not apply to 462
 all areas, of course, but those operating in many branches 463
 of medicine may find that their jobs have been superseded 464
 by chips. Technology has significantly altered the form and 465
 meaning of the medical relationship. Increasingly, technical 466
 aspects dominate the doctor–patient relationship. Now these 467
 aspects may even come to determine the possibility of indi- 468
 vidualising therapy. The appropriateness of using technical 469
 procedures as a way of dealing with societal problems is al- 470
 ways highly debatable, and this trend is one which needs to 471
 be carefully checked. 472

However, the paradox inherent in pharmacogenomics is 473
 that technological medicine is creating a new personalised 474
 medicine. There is a certain irony in this, considering that 475
 one of the main outcomes of the genetic revolution will be to 476
 see an aphorism often used to criticize modern technological 477
 medicine come true, that is, that you should treat the patient, 478
 not the disease—or, at least, that you can and should tailor 479
 treatment to the patient. This perhaps will have us remember 480
 that, as usual, *there are more things in heaven and earth* 481
than are dreamt in our philosophy! 482

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