

# INFORMATION FOR DOCTORS ORDERING A PERSONAL GENOME SEQUENCE FROM ILLUMINA

Thank you for your interest in ordering a Personal Genome Sequence from Illumina. This document will provide you background information on:

- Personal Genome Sequence
- Illumina's sequencing technology and the sequence it generates
- All the steps necessary to receive a patient's personal genome sequence
- Potential medical significance of the personal genome sequence
- Some ethical matters to be aware of
- The consent form
- Additional ethical issues
- The role of a Genetic Counselor in the process
- Indications for advising patient against personal genome sequence
- Bibliography of peer-reviewed articles
- Frequently asked questions
- The best way to contact Illumina regarding the personal genome sequence service

## PERSONAL GENOME SEQUENCE

[Excerpt from the patient consent form] The Personal Genome Sequence your patient will receive will be in the form of an electronic file containing the best estimate of the sequence of DNA in the cells (i.e., blood sample) your patient submitted. This sequence of chemicals is represented by four letters (A,C,G,T) that comprise the four types of bases found in DNA. One copy of a genome contains about 3 billion bases, or letters. In fact each person has two copies, one inherited from each biological parent. These letters represent the unique sequence of DNA in each of your cells, and your body uses these as the master instructions for many processes that happen in the cells of your body. The DNA sequence information we will deliver will not cover 100% of your genome—some part of your genome will not be sequenced.

The electronic file delivered will also contain information regarding locations in your DNA sequence where a Single Nucleotide Polymorphism (SNP) may be present. Each cell typically has two copies of each chromosome, one from each parent (see above). When either copy has a different base at the same location relative to each other, or to the published human genome reference sequence, that location is called a SNP. SNPs comprise genetic differences between individuals that occur at 0.1% of all bases in the genome, and so represent one source of the genetic information that is variable among all humans. Another source of genetic variation arises from loss, gain or changed order of one or more bases in your genome. Some of that variability (but not all) contributes to differences in disease risks, drug responses, phenotypic or physical appearance, etc.

## ILLUMINA'S SEQUENCING TECHNOLOGY AND THE SEQUENCE IT GENERATES

At Illumina, we extract the patient's DNA from the blood sample that is provided to us. We break the DNA into around 500 million small pieces and attach them to the surface of small glass microscope slides. We determine the sequence of all the pieces (typically 150–200 bases each) simultaneously. All the pieces are then assembled together to make the whole genome sequence. This is then compared to the public human genome reference sequence to look for differences and define the SNPs and other features that constitute your individual genetic make-up. We store all the sequence and the results of the comparisons in a secure computer. The assembled version of the sequence is loaded into a visual display program. This makes it possible to view the sequence and to see the positions of important features, including genes, SNPs and other sources of genetic variation.

To ensure that we determine the patient's personal genome sequence as accurately and completely as possible, we determine the identity of each base in the sequence 30 times on average, to check that we have covered all the bases and to be sure we have the right answer at every position.

## STEPS NECESSARY TO RECEIVE A PATIENT'S PERSONAL GENOME SEQUENCE

In Appendix A is a schematic of the steps involved in ordering, collecting the sample, receiving the personal genome sequence and delivering it to the patient. Illumina will provide specific documents and materials at each step of the process to support you. These include a consultation script to help you and/or the Genetic Counselor while reviewing the consent form with the patient and advising your patient on the benefits and risks of getting a personal genome sequence.

## POTENTIAL MEDICAL SIGNIFICANCE OF PERSONAL GENOME SEQUENCE

A patient's personal sequence information will include data on all variants that he or she carries, some of which may be of known significance (that is, have been clinically validated as being related to specific diseases or conditions). However, while personal genome sequence data are technically accurate to specifications described in the section on scientific and technical aspects above, personal genome sequence is not a clinically validated test and should not be used medically as such.

Instead, personal genome sequence data can be used as an indication to order clinically validated tests for specific variants of known significance. Patients also can be advised of the availability of consumer services that have developed algorithms to calculate aggregate risks for specific diseases based on the presence of multiple variants that have been associated with those disorders. However, both you and your patient should be aware that those risk estimations are not clinically validated, and often include both known variants and suspected variants. In addition, it will be important to counsel your patient about the minor contribution that most known variants make to complex diseases such as diabetes, heart disease, and cancer as well as the potential implications of variants in your patient's genome for the genomes of parents, siblings, and offspring. You and your patient also may want to develop a plan for periodically reviewing personal genome sequence data to take into account new scientific discoveries and changing medical guidance for estimating genetic contributions to risks for specific diseases and conditions.

## ETHICAL MATTERS TO CONSIDER

A number of ethical issues are outlined in the consent form and the accompanying suggested script for discussing the consent form with your patient. Most of those issues are primarily of relevance to

your patient. Two ethical issues of greatest relevance to your relationship with your patient are the privacy of the sequence data that you will order and review with your patient, and any obligation you may feel to encourage your patient to disclose findings of variants known to have high penetrance to close biological relatives who may carry the same variants.

Your office will receive your patient's personal genome sequence data and be responsible for maintaining its privacy while in possession of it. The risks from breaching the privacy of personal genetic data are unknown, but could include adverse implications for your patient's employment, insurability, and reputation, and also for those of his or her biological family members. You should consider whether you feel an obligation to hold a copy of the personal genome sequence data after you have reviewed it with him or her. As long as you have possession of the personal genome sequence data, you have a responsibility to maintain its privacy and should discuss with your patient how your office protects private health information. Second, you should consider what indications in the personal genome sequence data should be noted in your patient's medical records as suggesting medically significant disease risks. You should discuss with your patient whether any third party such as your patient's health insurer might have access to that medical record and also discuss how your office maintains the confidentiality of medical records.

Some patients' personal genome sequence data may indicate the presence of highly penetrant variants, such as the mutation that causes Huntington's disease in all cases in which it is present. While the personal genome sequence data are not clinically validated to diagnose such genetic disorders, you will no doubt advise your patient about the availability of validated clinical tests on which such diagnoses could be made. You also may feel some obligation to strongly encourage your patient to disclose the potential for carrier or affected status to their close biological relatives. This is an obligation that you should discuss with your patient in the context of discussing the availability of a validated clinical test for the disorder in question. There is a large medical ethics literature on the subject of such obligations to disclose, and you should consult that literature as well as local bioethics experts to determine your appropriate course of action.

## CONSENT FORM

The consent form and the recommended consent script are designed to make your patient understand that personal genome sequencing should not be treated as a medical test and that there are a number of limitations and ambiguities in the significance of the data returned, including the limited extent to which genes alone influence one's health. The consent form also outlines a number of present and future risks in obtaining one's personal sequence. We ask you to use your professional experience and judgment to ensure that any patient for whom you write a personal genome sequence order understands these issues. Personal genome sequence could be considered more harmful than beneficial for patients who hold unrealistic expectations about the utility of their sequence information for health and other purposes as well as for those who do not demonstrate an awareness of the potential risks in having their sequence data. The recommended consent script provides explicit opportunities for patients to indicate to you that they understand these and other specific issues. Patients who do not evidence such understanding should not be advised to proceed with personal genome sequence.

## ADDITIONAL ETHICAL ISSUES

As noted throughout the materials provided for Illumina's personal genome sequence service, there currently is no comprehensive or systematic means for reviewing the massive amount of information in your patient's raw personal sequence data and identifying all known disease- and drug response-related

variants that may be found therein. Consequently, in ordering a personal genome sequence test for your patient, you are obtaining information that will be difficult for you to access and assess. Although patients are explicitly informed of this situation in the informed consent document, you should consider whether this limitation exposes you to any liability in the physician-patient relationship.

## **ROLE OF A GENETIC COUNSELOR**

In many respects, the decision-making process for personal genome sequence is similar to that for any genetic test. Patients should work through their family histories with a genetic counselor to identify any potential inherited diseases or conditions for which personal genome sequence might be informative. A significant difference, though, in the case of personal genome sequence is to use that family history to avoid treating personal genome sequence as a surrogate for any clinically validated genetic test that would normally be medically indicated by the patient's family history. If a clinically validated test is indicated in the course of taking the family history, then we strongly recommend that the patient be advised to take that clinically validated test and receive the results of it prior to going forward with personal genome sequence.

The genetic counselor also can work through the consent for personal genome sequence (using the provided suggested consent script) and serve as a resource for the patient in dealing with any questions or issues arising from it. The genetic counselor can assist in evaluating whether the patient is competent to give consent and also whether the patient has understood the issues raised in the consent form.

The genetic counselor also will be an important resource in assisting the doctor in helping the patient interpret the personal genome sequence data. Most of the variants in those data will be of unknown significance, and the genetic counselor can help the patient understand the extent to which many genetic contributors to disease or drug response are still being discovered. The genetic counselor also can help the patient understand the tentative nature of new genetic discoveries, the process of confirming them, and the threshold at which they become medically actionable. The genetic counselor can work with the doctor and the patient to develop a plan for periodically reviewing the personal genome sequence data for new discoveries and medical recommendations. With respect to indications of the medical significance of known variants found through personal genome sequence, the genetic counselor can assist in calculating disease risk estimates and educating the patient about the relatively small contribution that genetic variants make to the risks for most diseases or conditions. The genetic counselor also can discuss with patients lifestyle and behavioral changes that could reduce disease risks. Finally, genetic counselors can help patients decide about any clinically validated genetic tests that are indicated by personal genome sequence findings, and then facilitate those tests that patients decide to pursue.

## **INDICATION FOR ADVISING A PATIENT AGAINST PERSONAL GENOME SEQUENCE**

As noted above, personal genome sequence should not be used as a surrogate for clinically validated genetic tests, which can be evaluated through taking family histories.

Patients with serious chronic illnesses (or with close biological family members with such illnesses) should be cautioned that personal genome sequence data will not be a pathway to treatment or a cure, and those who pursue personal genome sequence with that goal primarily in mind should be counseled against undertaking personal genome sequence.

Patients who go through the consent process but continue to hold strongly deterministic and exceptionalist expectations about the contribution of genes to most diseases and disorders also should be counseled against undertaking personal genome sequence.

Other concerning indications may arise from doctor and genetic counselor interactions with a patient that suggest caution in proceeding with personal genome sequence. In general, these concerns would suggest that the patient has unrealistic expectations about the utility or meaning of personal genome sequence data.

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## FREQUENTLY ASKED QUESTIONS

### **Q: In what form will I receive my patient's personal genome sequence data?**

**A:** You will receive an iMac and encrypted hard drive loaded with your patient's personal genome sequence data as well as a visual display program. This program will allow you to view the sequence and to see the positions of important features, including genes, SNPs, and other sources of genetic variation. Be prepared to let your patient leave with the iMac and hard drive at the end of the counseling session.

### **Q: If I find a known variant in my patient's sequence data, can I proceed directly to take appropriate medical action (if any is available)?**

**A:** The personal genome sequence data are not clinically validated, so any indications of known variants in the personal genome sequence data should be followed up by ordering the appropriate clinically validated genetic test before any medical actions are taken. personal genome sequence testing should not be used as a surrogate for medically indicated, clinically validated genetic tests for known variants.

### **Q: Should I retain a copy of my patient's personal genome sequence data or enter personal genome sequence findings of known variants associated with specific diseases or disorders in my patient's medical records?**

**A:** This is something that you should discuss with your patient as part of the consent process for personal genome sequence testing. Because personal genome sequence data are not clinically validated, you may determine that it is inappropriate to enter personal genome sequence indications for known variants in your patient's medical records. At the same time, you could decide to treat personal genome sequence indications as you would other patient self-reports of possible symptoms and include those in his or her medical records as such. If you decide to include personal genome

sequence indications in your patient's medical records, you should discuss the potential for third-party access to those records with your patient beforehand. Similarly, if you decide to retain a copy of your patient's entire personal genome sequence dataset, you should discuss with your patient how you will store those data, how you will protect their privacy, the potential for third-party access to those data, and how you might use those data in the future as you care for your patient.

**Q: What are my obligations (if any) to my patient's close biological relatives about whom my patient's personal genome sequence data may be informative?**

**A:** This is a difficult ethical question to which there is no clear answer. Legally, you are under no obligation to inform your patient's close biological relatives about personal genome sequence findings that may affect their health, and doing so against your patient's wishes may violate your patient's privacy rights. At the same time, you certainly should discuss with your patient the implications for close biological relatives of personal genomic indications for known variants, and be prepared to assist your patient in discussing those findings with his or her biological relatives. There is an ongoing medical ethics literature on this topic, and the emergence of personal genome sequence testing will no doubt influence the future direction of ethical standards in this area.

**Q: How often should I review my patient's personal genome sequence data to take account of ongoing scientific discoveries and medical recommendations?**

**A:** Plans for periodic review of personal genome sequence data should be discussed with your patient as part of your consultation once the data are delivered. You may want to schedule an annual review as part of your patient's overall care plan.

**Q: Are personal genome sequence testing and my consultations with patients about it reimbursable?**

**A:** No. Because personal genome sequence testing is not clinically validated, neither the test nor your time is reimbursable. You should discuss a private fee arrangement with your patient to compensate you for the time you spend arranging the test, going through the consent process, and interpreting the personal genome sequence data.

## CONTACT INFORMATION

Because of the potentially confidential aspect of personal genome sequence, we ask that you do not use Illumina's general customer support and ordering hotline and emails. Instead, Illumina has setup a centralized and dedicated way to handle all matters related to personal genome sequence. Please use one of the three options below.

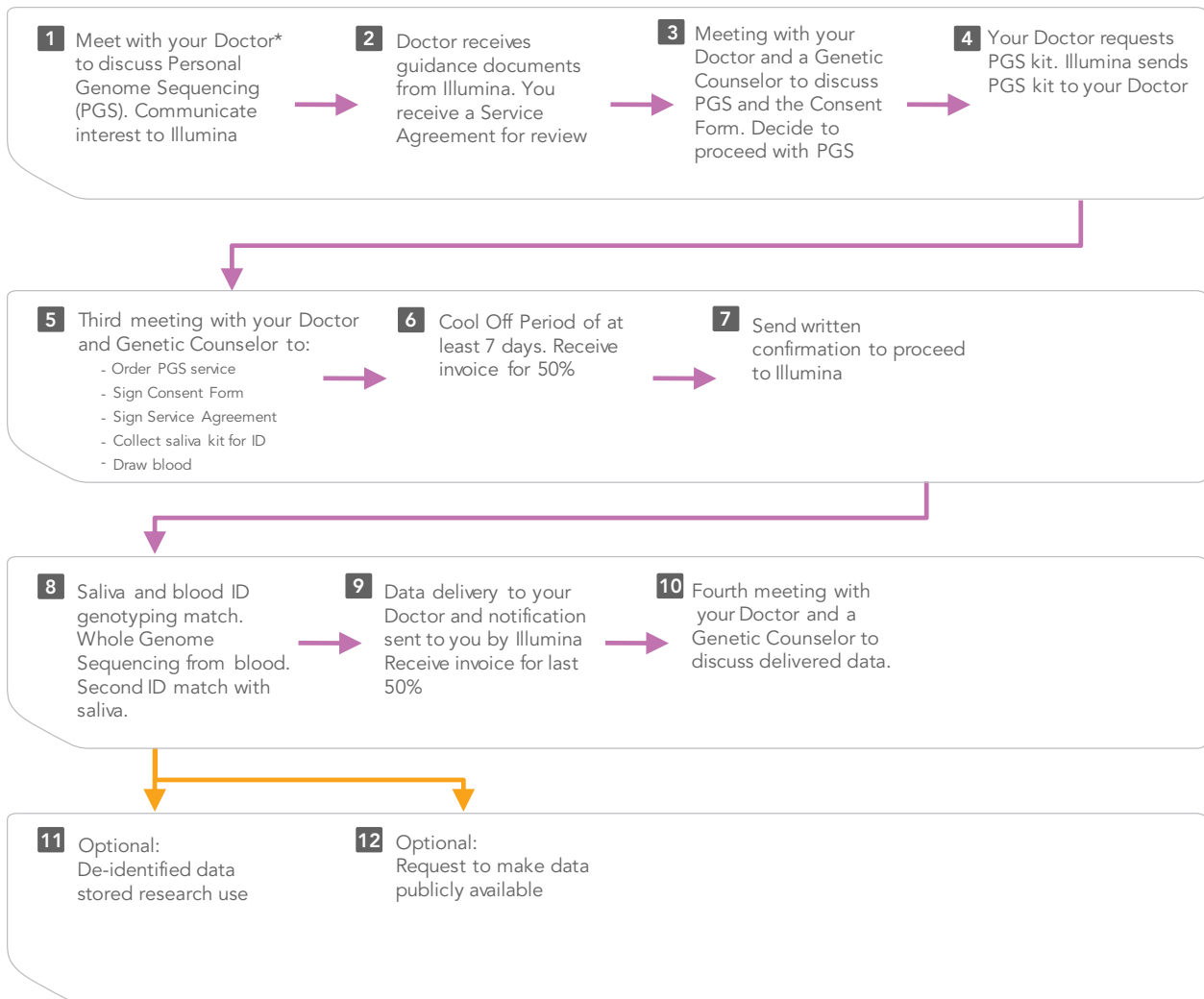
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## PERSONAL GENOME SEQUENCE PROCESS FLOW

**Note:** This schematic is presented from the standpoint of the patient. "You" refers to the patient him/herself, "send" or "receive" means that the patient sends or receives.



\*Doctor in this chart refers to your regular Doctor or a Medical Geneticist or both.