

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference <b>ILLINC346WO</b>	<b>FOR FURTHER ACTION</b>		See item 4 below
International application No. <b>PCT/US2017/055653</b>	International filing date ( <i>day/month/year</i> ) <b>06 October 2017 (06.10.2017)</b>	Priority date ( <i>day/month/year</i> ) <b>07 October 2016 (07.10.2016)</b>	
International Patent Classification (8th edition unless older edition indicated) <b>See relevant information in Form PCT/ISA/237</b>			
Applicant <b>ILLUMINA, INC.</b>			

<p>1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).</p> <p>2. This REPORT consists of a total of 11 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																								
<p>3. This report contains indications relating to the following items:</p> <table> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> <p>4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).</p>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
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	Date of issuance of this report <b>09 April 2019 (09.04.2019)</b>
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# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**  
(PCT Rule 43*bis*.1)

To:

see form PCT/ISA/220

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/US2017/055653

International filing date (day/month/year)  
06.10.2017

Priority date (day/month/year)  
07.10.2016

International Patent Classification (IPC) or both national classification and IPC  
INV. G06F19/18 G06F19/22

Applicant  
ILLUMINA, INC

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of this opinion

see form PCT/ISA/210

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:
  - the international application in the language in which it was filed.
  - a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2.  This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3.  With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
  - a.  forming part of the international application as filed:
    - in the form of an Annex C/ST.25 text file.
    - on paper or in the form of an image file.
  - b.  furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
  - c.  furnished subsequent to the international filing date for the purposes of international search only:
    - in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
    - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4.  In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	<u>1-27</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-27</u>
Industrial applicability (IA)	Yes: Claims	<u>1-27</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

- D1 US 2011/270533 A1 (ZHANG ZHENG [US] ET AL) 3 November 2011 (2011-11-03)
- D2 MILLER JASON R ET AL: "Assembly algorithms for next-generation sequencing data", GENO, ACADEMIC PRESS, SAN DIEGO, US, vol. 95, no. 6, 1 June 2010 (2010-06-01), pages 315-327, XP009165741, ISSN: 0888-7543, DOI: 10.1016/J.YGENO.2010.03.001

**Re Item V.**

**1 Art. 34(4)(a)(i) / Rule 67.1 PCT.**

Method claims 18-27 only contain mathematical steps and/or mental activities. No technical means for performing these steps are specified (Rule 67.1(i) and (iii) PCT).

In the following examination of this claim, it was assumed that the claim is intended to comprise technical means, in that the method is implemented using a system comprising a memory and a processor as in claim 1.

**2 Inventive step (Art. 33(3) PCT).**

2.1 Subject-matter of claim 1 comprises both technical and non-technical features.

For the assessment of claims comprising both technical and non-technical features, the corresponding passage of the Guidelines for Search and Examination at the European Patent Office as PCT Authority, section G-VII 5.4, is highly relevant, and accordingly the corresponding section in the Guidelines for Examination in the EPO applies mutatis mutandis. Thus in the following, reference is made to the corresponding passage in the Guidelines for Examination in the EPO.

**2.2 Assessment of inventive step of mixed-type inventions**

Claim 1 comprises technical and non-technical features.

The assessment of inventive step is therefore carried out in accordance with section G-VII, 5.4 of the Guidelines for Examination.

In the case of claims comprising technical and non-technical features, only those features which contribute to the technical character of the invention are taken into account for the assessment of inventive step.

### 2.3 Closest prior art and distinguishing features

D1 is considered to be a suitable starting point for the assessment of inventive step of claim 1 and is taken as the closest prior art.

D1 discloses (features not disclosed in D1 are ~~struck out~~ and labelled as a) - d) for later reference):

A system for sequencing polynucleotides:

a memory comprising a reference nucleotide sequence;

a processor configured to execute instructions that perform a method comprising:

**[0007], claim 1**

receiving a first nucleotide subsequence of a read from a sequencing system;

processing the first nucleotide subsequence using a first alignment path to determine a first plurality of candidate locations of the read on the reference sequence;

determining whether the first nucleotide subsequence aligns to the reference sequence based on the determined candidate locations;

**[00158], claim 1; wherein the feature of "using a first alignment path" is implicit under the assumption given below (3.3)**

receiving a second nucleotide subsequence from the sequencing system;  
processing the second nucleotide subsequence to determine a second plurality of candidate locations of the read that align to the reference sequence

**[00158], claim 1**

using:

a second alignment path if the read is aligned to the reference sequence, and

**implicit under the assumption given below (3.3)**

~~the first alignment path if otherwise,  
wherein the second alignment path is more computationally efficient than the first alignment path to determine the second plurality of candidate locations of the read.~~

- 2.4 The subject-matter of claim 1 therefore differs from the disclosure of D1 in the features that
- a) the determination of candidate locations for the second alignment is made, if the read is "not aligned", "using the first alignment path", and
  - b) wherein the second alignment path is "computationally more efficient than the first alignment path".

2.5 These features are however highly unclear (see 3.2 - 3.5), and for this reason alone cannot render claimed matter inventive.

2.6 Furthermore these distinguishing features – *when taken in isolation* – are all non- technical since they represent algorithmic steps, i.e. mathematical methods and/or mental acts, which represent non-inventions in the meaning of Rule 67.1 PCT.

Features which are non-technical when taken in isolation may nevertheless contribute to the technical character of an invention if, in the context of the invention, they contribute to producing a technical effect serving a technical purpose (Guidelines G-VII, 5.4, second paragraph).

In the present case, the distinguishing features do not contribute to the technical character of the invention for the reasons following.

2.7 The purpose which these distinguishing features *allegedly* serve in the context of claim 1 is "sequencing polynucleotides".  
If understood as the *determination of the sequence of a nucleic acid*, this can be considered a technical purpose.

However, the claim only describes (and only vaguely so) some steps which are *involved* in the *alignment* of nucleic acids, wherein potentially some "candidate locations" for a first or second read are obtained. This is far from the actual determination of a specific nucleic acid sequence.

2.8 Thus, the distinguishing features which process the technically derived data (i.e. the sequencing reads) in order to serve the above-mentioned technical purpose are not defined in sufficient detail, and - as detailed below (3.1 - 3.5) with many deficiencies.

The stated deficiencies deprive the skilled reader of the information he/she needs to understand how to proceed from the input data - i.e. several reads - through the remaining steps to arrive at a specific technical solution, namely at a specific and correct genomic sequence.

Under these circumstances, no interaction can be established between the technical data and the non-technical features achieving the above-mentioned technical purpose. The distinguishing features, which pertain to a general manner of data analysis, do thus not contribute to the technical character and are to be ignored in assessing inventive step.

- 2.9 Alternatively, if claim 1 is read as providing a system for *aligning sequences*, such a system does not serve a technical purpose since an alignment (similar to a comparison of text, numbers etc.) does not have a technical effect. Also in this case, the algorithmic features of the claim cannot be considered in the assessment of an inventive step, since they do not contribute to a technical effect.
- 2.10 As claim 1 does not comprise any feature making a technical contribution over the teaching of D1, it cannot be regarded as involving an inventive step within the meaning of Article 33(3) PCT (G-VII, 5.4(iii)(b)).
- 2.11 The same reasons apply, *mutatis mutandis*, to the method of claim 18 (see also 3.7 below).
- 2.12 Similarly, none of the dependent claims 2-17 and 19-27 can be considered inventive over the prior art. Also these further features are not defined in sufficient detail, and with many further deficiencies (see 3.6, 3.7), so that they do not allow the skilled reader to understand how to proceed from the input data to arrive at the determination of the genomic sequence.
- 2.13 For similar reasons, all claims lack an inventive step over D2. D2 reviews several methods and corresponding computer programs for sequence assembly from short reads (throughout, e.g. abstract). The use of computer systems comprising a memory and processor is herein necessarily implicit. Also, the methods involve receiving a plurality of (i.e. at least first and second) reads, and aligning them to a reference, wherein the use of "alignment paths" is implicit (see also 2.3 and 3.3). Moreover, also the graph-directed assembly (D2 pg. 317, 318) of multiple reads can be considered as an involvement of "alignment paths".

Thus also with respect to D2, claim 1 differs in features a) and b) as outlined in section 2.4. As detailed above (2.5 - 2.9), these features are not only highly unclear, but the steps to be carried out by the system are also not described with sufficient detail and with many further deficiencies, so that these features cannot contribute to the technical character of the invention,



- 2.14 As claim 1 does not comprise any feature making a technical contribution over the teaching of D2, it cannot be regarded as involving an inventive step within the meaning of Article 33(3) PCT (G-VII, 5.4(iii)(b)).  
The same applies to the systems of dependent claims 2-17, and to the methods of claims 18-27.

**Re Item VIII.**

**3 Clarity (Art. 6 PCT).**

- 3.1 Numerous expressions in the claims are unclear. In particular, several features are only defined in the **desired result**, but not the technical features required for achieving the result.  
It should be noted that the mere statement that certain, moreover vaguely defined, general steps or features should be "somehow involved" in a particular operation, does not clearly define the input or output of this operation, and most importantly not the actual steps to be carried out. This applies especially to the following definitions of claim 1:
- 3.2 - "processing the first nucleotide subsequence according to a first alignment path":  
There is no clear and unambiguous definition in the art of an "alignment path", let alone what "processing according to an alignment path" may include or exclude.  
The skilled reader could only *assume* that it was meant to refer to an alignment according to a Smith-Waterman (or Needleman-Wunsch) algorithm, wherein one or more "paths" through a similarity matrix of the sequences to be aligned are identified.  
However this is not unambiguously clear from the claim, nor would such a (partial) explanation fit with the terms of the claims, since such Smith-Waterman "paths" are specific for the sequences to be aligned, and thus cannot be applied to other alignments (see also 3.4).
- 3.3 - "determine whether the first nucleotide sequence aligns to the reference sequence based on the determined candidate locations":  
This sentence obscures the actual meaning of the word "align" as used in the claims. As understood in the art, an "alignment" is just a comparison of sequences, wherein no defined limit to the degree of similarity exists. Thus, any two given sequences will *always* "align", however with varying degrees of similarity. This is also evident from the claim, in that one or more "candidate

positions" are obtained. Thus, it appears that the applicant considers the word "align" to relate to a *specific* alignment, however it is not clear which one this may be nor how to determine this "based on the determined candidate locations".

- 3.4 The same objections (3.2, 3.3) apply to the "processing" of the second nucleotide subsequence. Moreover, it is entirely unclear how, following an alignment, the two sequences should be determined *not* to be aligned ("[...] if the read is aligned [...] otherwise [...]"), and how an "alignment path" (if interpreted as a "path" through a matrix in a Smith-Waterman alignment algorithm) from a first nucleotide subsequence should be used for aligning a second, potentially entirely unrelated subsequence.
- 3.5 The expression "wherein the second alignment path is more computationally efficient" (besides the fact that only a method, but not a "path" or other kind of data can be "efficient") describes a desired effect, but not the steps necessary for achieving it (cf. EPO PCT Guidelines F-IV 4.10).
- 3.6 Also the dependent claims comprise numerous unclear formulations:
- In claim 2, it is not clear what kind of "alignment quality metric" is meant, and how the nucleotide subsequence should be processed "based on" it;
  - the features of claims 3, 4, 6 and 7 are necessarily implicit to claim 1, and thus not further limiting and obsolete;
  - claim 5 defines steps by a desired result, rather than the features necessary for achieving it;
  - in claims 8 and 9, it is not clear how a "simple alignment" should be different from another alignment;
  - in claim 12 it is not clear how the "variant calling" using a plurality of candidate locations should be carried out;
  - in claim 13, it is not clear what a "variant calling path" may be, and the claim also defines steps by a desired result, rather than the features necessary for achieving it.
- 3.7 The same objections apply to claims 18-27. In addition, it is not clear what a "secondary analysis" may be or what effect this should have.

- 3.8 It is noted that it is not sufficient for the requirement of clarity if the reader could gain, from certain passages of the description, an understanding of what might potentially be meant by unclear expressions in the claims. Moreover, in the present case even the specific examples ([0052]-[0057]) do not seem to render the above expressions any clearer.