UNITED STATES	PATENT AND TRAD	DEMARK OFFICE
BEFORE THE PA	ATENT TRIAL AND A	APPEAL BOARD

TWINSTRAND BIOSCIENCES, INC. Petitioner,

v.

GUARDANT HEALTH, INC. Patent Owner.

Case IPR2022-00747 U.S. Patent No. 10,889,858

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,889,858

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Patent Trial and Appeal Board U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450



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	A.	Optimization techniques for DNA library preparation were well known.	3
	B.	Cell-free DNA isolated from blood was widely used in next-	_
		generation sequencing platforms. 1. The presence of cell-free tumor DNA in human blood was well known.	
		2. Isolating cfDNA from blood was routine with commercially available kits.	
	C.	The prior art taught that Duplex Sequencing could dramatically lower the error rate of NGS	
	D.	The prior art taught applying Duplex Sequencing to cfDNA	
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IX.		nd 1: claims 1-7 and 10-27 would have been obvious over Murta	
	A.	Claim 1	26
		1. "A method for analyzing sequencing reads of double-stranded cell-free deoxyribonucleic acid (cfDNA) molecules from a sample of a subject"	. 26
		2. "(a) tagging a plurality of double-stranded cfDNA molecules from a population of double-stranded cfDNA molecules from the sample with a set of library adaptors comprising a plurality of molecular barcodes to generate tagged parent polynucleotides, wherein the	



	adaptors from the set of library adaptors to the plurality	
	of double-stranded cfDNA molecules from the	
	population using more than a 10× molar excess of	
	library adaptors as compared to the double-stranded	26
2	cfDNA molecules of the population"	26
3.	"wherein the tagging produces at least 20% of the	
	double-stranded cfDNA molecules of the populations having library adaptors ligated to both ends of a	
	molecule of the double-stranded cfDNA molecules"	28
4.	"(b) amplifying a plurality of the tagged parent	20
т.	polynucleotides to produce progeny	
	polynucleotides"	29
5.	"(c) sequencing a plurality of the progeny	2 9
	polynucleotides to produce a set of sequencing	
	reads"	29
6.	"and (d) determining, based at least on sequence	
	information from the molecular barcodes, individual	
	double-stranded cfDNA molecules from among the	
	tagged parent polynucleotides for which either (1) both	
	a Watson strand and a Crick strand of the individual	
	double-stranded cfDNA molecule are detected or (2)	
	only one of a Watson strand or a Crick strand of the	
	individual double-stranded cfDNA molecule is	
	detected from a plurality of sequencing reads from the	
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0	Schmitt, and Meyer.	32
8.	A POSA would have had a reasonable expectation of	26
Claim	success	
1.	"A method for analyzing double-stranded cell-free	39
1.	deoxyribonucleic acid (cfDNA) molecules from a	
	sample of a subject"	39
2.	"(a) tagging a plurality of double-stranded cfDNA	
2.	molecules from a population of double-stranded	
	cfDNA molecules from the sample with a set of library	
	adaptors comprising a plurality of molecular barcodes	
	to generate tagged parent polynucleotides, wherein the	
	5 55 1 1 7	



B.

	tagging comprises ligating a plurality of library	
	adaptors from the set of library adaptors to the plurality	
	of double-stranded cfDNA molecules from the	
	population using more than a 10× molar excess of	
	library adaptors as compared to the double-stranded	
	cfDNA molecules of the population"	39
3.	"wherein the tagging produces at least 20% of the	
	double-stranded cfDNA molecules of the population	
	having library adaptors ligated to both ends of a	
	molecule of the double-stranded cfDNA molecules"	40
4.	"(b) amplifying a plurality of the tagged parent	
	polynucleotides to produce progeny	
	polynucleotides"	40
5.	"(c) determining nucleotide sequences of a plurality of	
	the progeny polynucleotides"	41
6.	"(d) analyzing a plurality of the nucleotide sequences	
	with a programmed computer processor the analyzing	
	comprising mapping a plurality of the nucleotide	
	sequences to a reference sequence to produce mapped	
	sequences"	41
7.	"grouping a plurality of the mapped sequences into	
	families based on a combination of sequence	
	information from the molecular barcodes and start and	
	stop positions of the mapped sequences, wherein a	
	family of the families is representative of an individual	
	double-stranded cfDNA molecule from among the	
	tagged parent polynucleotides"	41
8.	"and identifying a plurality of the families as having	
	nucleotide sequences representing either (1) both a	
	Watson strand and a Crick strand of an individual	
	double-stranded cfDNA molecule from among the	
	tagged parent polynucleotides or (2) only one of a	
	Watson strand or a Crick strand of an individual	
	double-stranded cfDNA molecule from among the	
	tagged parent polynucleotides."	
	s 2 and 17	
	s 3 and 18	
	s 4 and 19	
Claire	as 5 and 20	10



C. D. E. F.

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	\mathbf{C}	Claims (and 7	40
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