Do my genes fit?
An overview into how the understanding of the genomics of gastric cancer can affect the different treatments received.

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1 Report Introduction

The following report has been designed to provide an understanding of how patients suffering from stomach or gastric cancer can receive different treatment based on the genomics of their cancer. **Section 2** of this report will focus on an introduction to gastric cancer aimed to the language level of a lay person. Any medical terms that were used will initially be *italicized* and immediately explained, all subsequent usage of that term will then take normal script. **Section 3** will first of all focus on an [Introduction to Cancer Genetics (3.1)](#), this section will provide a background in genetics that will be necessary for understanding the complexities used in the latter parts of **section 3**, (**3.2 - 3.7**). **Section 3.2** will outline the largest genomic experiment to date regarding gastric cancer conducted by The Cancer Genome Atlas. **Sections (3.3-3.7)** concern the 4 different classes of gastric cancer, based on their genomics. An explanation will be provided about the genomic deficits in each class before describing the therapies used.

2 Overview of Gastric Cancer

2.1 Epidemiology

Gastric cancer or Stomach cancer is the 16th most common cancer in the United Kingdom, with 7,067 patients newly diagnosed with gastric cancer every year. (1) Stomach cancer affects men slightly more frequently than it affects women (18:10). (1) Gastric cancer is an age specific disease with over half (51%) of incident cases in 2013 being diagnosed in those over 75. The peak incidence of gastric cancer is in the 85-89 age bracket. (1)

The rate of gastric cancer varies between countries, with a greater proportion of people being affected in East Asia, East Europe and South America, in contrast North America and parts of Africa show the lowest rates of gastric cancer. (2) However interestingly in the United Kingdom Asian males and Asian females are at a lower rate of gastric cancer compared to White and Black British people (5.2 to 8.5 per 100,000 vs 14.1 to 14.7 per 100,000 (White), and 16.1 to 25.6 per 100,000 (Black). (1)

2.2 Introduction: Risk factors of gastric cancer

The risk of getting any particular cancer can be divided into *modifiable* (factors that can be changed) and *non-modifiable* risk factors (which can’t be changed i.e gender, ethnicity, etc). Modifiable risk factors include alcohol consumption, obesity, lower socioeconomic status, smoking tobacco and a diet that consists of excessive salted, pickled or cured foods. (3) Furthermore an important modifiable risk factor is infection with *H. pylori*, which is a type of bacteria which can live in the digestive tract. (4) *H. pylori* is believed to cause a two-threefold increase in the risk of gastric cancer by causing *chronic gastritis* (which is long term inflammation of the stomach). (4)(5)(6) Chronic gastritis is present in a large population of patients with stomach cancer and is a risk factor for gastric cancer. (4)

Non-modifiable risk factors include previous surgery to remove parts of the stomach, if there are fewer acid producing parts of the stomach it is more likely that certain bacteria can grow in the stomach and cause inflammation of the stomach cells which can lead to cancer. Other diseases called *Pernicious anaemia* (a disease where sufferers are deficient in Vitamin B12) and *anhydrochloria* (an inability to produce stomach acid) have an increased predisposition to gastric cancer. (3) (7) Furthermore having a first degree relative (parents, siblings or children) who has had stomach cancer increases an individual’s chances of having stomach cancer. (3) There are several genomic conditions that are associated with an increased risk of gastric cancer, which will be discussed in more detail later.
2.3 Staging of Gastric Cancer

Staging refers to the size of the tumour and if it has spread outside the stomach. Staging is commonly scored using the\textbf{TNM} system. Where \textbf{T} refers the size of the tumour and how far it has spread inside the stomach, \textbf{N} refers to if the cancer has spread to any nodes and \textbf{M} refers to if the cancer has metastasised/spread to a different site.

If the cancer is confined to the innermost layers of the stomach (the \textit{mucosa and submucosa}) it is called a \textbf{T1 cancer}.

If the cancer has penetrated into the muscle layer (\textit{muscularis mucosa}) of the stomach, we call this a \textbf{T2 cancer}.

When the cancer penetrates through to the outermost stomach lining but not through the lining, we call this a \textbf{T3 cancer}.

When the cancer penetrates right through the outer lining of the stomach we call this a \textbf{T4 cancer}.

The ‘\textbf{N}’ part of the score refers to how many regional nodes of the stomach we can detect the presence of cancer cells. This can be divided into \textbf{N0} (0 nodes affected), \textbf{N1} (1 or 2 nodes affected), \textbf{N2} (3 to 6 nodes), \textbf{N3a} (7-15 nodes) and \textbf{N3b} (16 or more nodes affected).\cite{8}

The ‘\textbf{M}’ part of the score refers to metastatic spread, if the cancer affects other organs (\textbf{M1}) or does not affect any other organ (\textbf{M0}).\cite{8}

2.4 Signs and Symptoms of Gastric Cancer

Stomach cancer symptoms can be divided into \textit{early onset symptoms} and \textit{symptoms of advanced disease}. Early onset symptoms are found when the patient initially suspects that there is something sinister going on and these symptoms include increased acidity in the stomach, increased burping feeling full which eventually leads to loss of appetite and weight loss.\cite{9, 10} Furthermore other early onset symptoms include bleeding in the stomach, this leads to a loss of red blood cells (\textit{clinically this is called anaemia}). Anaemia makes patients feel tired and breathless.\cite{9, 10} Furthermore due to the increased bleeding in the stomach, there is an increased predisposition to clot to control the bleeding; the patient may experience sudden pain in the chest or leg caused by a clot.\cite{9, 10}

The symptoms of advanced stomach cancer include unintentional weight loss, fluid in the abdomen if the cancer spreads to the liver (\textit{ascites}) and blood in the stools or blood in the vomit.\cite{9, 10}

2.5 Diagnosis of Gastric Cancer

Gastric cancer should be diagnosed by an \textit{endoscopic biopsy} (a tube put down into the stomach, which will allow the operating surgeon to take specimens).\cite{11} Other initial investigations could include full blood count to check for anaemia, liver and kidney function tests. Staging is determined by computed tomography (CT) of the thorax, abdomen and pelvis; which looks for the presence of spread of the cancer.\cite{11}
2.6 Treatment of Gastric Cancer

The treatment for stomach cancer is dependent on whether we consider the cancer operable or non-operable. If a cancer is operable; it is said that a patient may be cured with surgery, however if a cancer is inoperable; surgery alone will not be able to cure the cancer. The type of surgery someone can receive can range from endoscopic resection of the tumour (where a tube is put into the stomach and the tumour is removed) to subtotal or total gastrectomy (this is where part or the entire stomach is removed). Chemotherapy or radiotherapy can be given before (neo-adjuvant) or after (adjuvant) surgery and this is useful in shrinking the tumour and eliminating any tumour cells that surgery was not able to remove.

Chemotherapy with or without radiotherapy in a palliative manner is the first treatment used in patients who have metastatic or inoperable disease. We use these therapies in a palliative manner, (this means that we are not trying to cure the patient of the disease but improve the quality of life, by improving control of symptoms). There are many different chemotherapeutic agents, and many studies have suggested various combinations of these drugs will be useful in curing disease.(14) (15) (16) Cancer cells are known for growing and dividing quicker than cells without cancer, and so chemotherapy is used to try and stop cancer cell division by damaging the genetic material in the cancer cells and cause the death of the cells. While chemotherapy has been a standard cancer treatment for decades, it is not without risks, by targeting cancer cells that divide quickly, as a side effect of the drug, normal cells that naturally divide at a rapid rate like hair follicles are also damaged and this can lead to hair loss.(17) Chemotherapy also severely depletes the immune system and leaves the patient open to many infections.(17) As such better treatment options with fewer side effects are needed so that we can target the cancer cells without damaging the healthy cells. These therapeutic options are an example of personalized medicine where the decision with regards to what therapeutic agent is used, depends on the patient. One of the key ways in which we can decide on what therapeutic agent to use depends on the genetics of a patient’s tumour.
3 Cancer Genetics and the Genomics of Gastric Cancer

3.1 Basic Introduction to Cancer Genetics

Understanding of genetics is essential to understanding personalised medicine and how we can develop very specific therapeutic agents to fight cancer. Our organs are formed by many proteins, these have been coded for by genetic material in our cells. The genetic material in humans is called Deoxyribose Nucleic Acid (DNA) and was discovered by Watson and Crick in 1953. DNA is found in a double helix strand (Figure 3) where the different strands are held together by different bases forming bonds together; adenosine usually binds to thymine, while cytosine will usually bond to guanine (19).

Ribosomes (cell structures that make proteins) use RNA like a code to make a protein. Only one strand of DNA is converted to RNA which is a messenger molecule that is used to make proteins. This is done in a process called transcription, where a special protein called RNA polymerase will separate the DNA helices. One of the strands the ‘sense strand’ is used as a template for the RNA. The RNA strand is read 3 bases at a time by the ribosome, in a process called translation, the information stored in the RNA is converted to information telling what protein to make. DNA is said to be redundant, this means that different combinations of 3 bases can lead to the same protein being made. (20)

Cell division is not always perfect and sometimes the cell structures involved with replication produce random errors and this will in turn produce errors in the DNA. Sometimes there may be an error in the base sequence of the DNA, where one base will mutate into another base. This process is called base substitution. Due to the nature of DNA, a base substitution can produce a synonymous mutation, where there is no difference in the protein produced or a non-synonymous mutation where a different protein is produced. (20) In severe cases this can cause the STOP protein, which will cause a premature end of the protein translation which can have functional consequences. This type of mutation is called a non-sense mutation. Sometimes DNA may be deleted or additional DNA may be inserted into the DNA sequence and this will also have similar effects to base substitutions. It is important to note that not all of our DNA codes for a protein, DNA is divided into exons (DNA material that can code for protein) and introns (DNA material that does not code). (20) There are often repeated parts of the DNA sequence, and various genomic sequencing experiments have been conducted to see how often a particular part of DNA is repeated in the average population. If there is a significant deviation from the average value the patient is said to have a copy number variation. (20)
Genes that are involved in cancer can be classified into *Tumour Suppressor genes*, (which prevent cancer formation by preventing faulty DNA being translated) and *Proto-oncogenes* (which cause the cell to proliferate). Human DNA is stored on chromosomes, a particular point on a chromosome where a particular gene is, is called the *locus*. We have 23 pairs of chromosomes, we get one pair from our mother and one from our father. As such at a particular locus, each gene will have two *alleles* (the genes inherited from our parents).

Certain alleles can behave in a *dominant* manner, this means that if that particular allele is present, it is irrelevant what is on the other chromosome, and that allele will be expressed at the genetic loci. However other alleles work in a recessive manner, this means that both alleles need to be the same for that allele type to be expressed.

In *certain hereditary cancer syndromes*, which are syndromes that predispose to developing cancer. Children will inherit a mutated/faulty allele from one of the parents. In tumour suppressor genes, this does not automatically mean the child will have cancer as they have a normal (*scientifically called Wild-Type*) allele that behaves in a dominant way and preserves the function of the Tumour Suppressor gene. As we have established random mutation can occur in DNA, as the children have already one copy of the faulty allele, they only need One mutation to have no functional alleles. As a result they are more likely to develop cancer than people without hereditary cancer syndromes. *(Figure 4)*

### 3.2 Inherited Cancer syndromes

While we have established that having a first degree relative who suffers from gastric cancer, increases an individual’s likelihood of developing gastric cancer. The most significant of these is *Hereditary Diffuse Gastric Cancer*, this disease carries such a predisposition to inheriting gastric cancer that a *total gastrectomy* (total surgical removal of the stomach) is recommended in a subpopulation of sufferers. This inherited syndrome carries a mutated copy of the *CDH1* gene, which is involved in cell adhesion (cells sticking together). *(21)* *(22)*

*Certain cancer syndromes that increase the risk of colon cancer, also increase the risk of gastric cancer; these included Familial Adenomatous Polyposus (a condition where hundreds of polyps form in the colon, which will eventually lead to cancer) and Hereditary Non-polyposus Colorectal Cancer (colorectal cancer which is formed from one polyp).*(21) While women who suffer from *Hereditary Diffuse Gastric Cancer* have an increased risk of breast cancer, in families who have a genetic predisposition to breast cancer (i.e the family will inherited a mutated copy of *BRCA1/BRCA2*) there is also an increased risk of gastric cancer.(21)

Furthermore *Li-Fraumeni* syndrome is also associated with an increased risk of gastric cancer, where it will affect people at a younger age.(21) *(23)*

*Li-Fraumeni* syndrome is characterised by a mutation in a gene called *TP53*, this gene is very important and is called the ‘guardian of the genome’ as it stops the cell replicating its DNA if there is an error.(21) *(24)* *(25)*

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*Figure 4: Knudson’s two hit hypothesis*:

Knudson’s two hit hypothesis is the formal name that describes the mechanism of why people who inherit a mutated allele as part of an inherited cancer syndrome are more likely to develop a tumour than people who are born with two wild-type or normal alleles.
3.3 The genomic profile of Gastric Cancer.

The Cancer Genome Atlas (TCGA) have conducted a genomic sequencing experiment on 295 patients who were not exposed to either chemotherapy or radiotherapy, as these processes would have changed the DNA. From this sample TCGA divided the tumours into two cohorts, those that were hypermutated (i.e. had a lot more mutations than the other tumours) and non-hypermutated. When the hypermutated tumours were analysed they found 10 genes were significantly mutated, i.e. mutated at a higher level than is seen across the normal population. Furthermore an additional 27 genes also had insertion/deletion mutations. Of the genes found to be significantly mutated in the hypermutated tumours we find several genes known to be associated with cancer, such as; ERBB3, PTEN and TP53. Several of these genes were found to be mutated at a higher rate in the 215 non-hypermutated tumours, other genes that were significantly mutated include KRAS, which is a proto-oncogene and also PIK3CA, which is a tumour suppressor gene.

TCGA divide gastric cancer into four different subtypes. The first subtype of tumours include tumours in which we can detect the presence of the Epstein-Barr virus, these tumours are known as Epstein-Barr positive tumours. The second type of tumour are known as microsatellite unstable tumours. They are known as this because there are mutations in the genes that are responsible for recognising errors in the DNA, these genes are the so-called microsatellite genes. Due to the mutations in the microsatellite gene, this results in a tumour with a very unstable genome and a high mutation rate. This is in stark contrast to the third set of tumour called the genomically stable tumours. The last set of tumours includes the tumours with chromosomal instability. Several of the tumours in this subtype have an abnormal number of chromosome, called aneuploidy.

3.4 EBV Positive Gastric Cancer

3.4.1 Genomic Analysis

Genomic Sequencing experiments confirm the presence of the Epstein-Barr virus in 9% of gastric tumours. While some cancers caused by the Epstein-Barr virus tend to affect people in less economically developed countries, (for example Burkitt’s lymphoma predominantly affects people in sub-Saharan Africa,) EBV positive gastric cancers are found all over the world. EBV positive gastric cancer has a very favourable outcome, compared to other sub-types. While the mechanisms for EBV positive gastric cancer are dubious, there is evidence about what genes are commonly mutated. There is a mutation in PIK3CA which is a known cancer gene. Mutations in the gene, cause the cancer cell to keep on growing and making more copies of itself. There is also an amplification of JAK2, this gene is commonly found in certain blood conditions which cause an excess of Red blood cells or Platelets (which are the cells that cause blood to clot).

Our DNA does not sit in its double helix structure in the cell, in fact it is wrapped around several proteins, which interact with the genes. Genes can be switched on and off, via special parts of DNA called promoter regions, which promote the DNA being transcribed into RNA which is then translated into a protein. There are many ways in which these promoter regions can be turned on and off, and one such way is called methylation. In this process a certain molecule called a methyl group will bind to the promoter region, and through their interaction turn a promoter region on or off. (Figure)
In EBV positive tumors a process called hypermethylation occurs where genes are turned off in an uncontrolled way (27). One important gene is $CDNK2a$, this gene encodes for two proteins that help regulate the cell cycle. When this is mutated the cancer cell will keep growing and will pick up more and more mutations.

3.4.2 Targeted Therapy directed against EBV positive Tumours

Now that the genomics of EBV positive Gastric Cancers are understood we shall discuss how we can specifically target these cancers. As the virus is present in all the cancer cells, it may seem strange why our immune system does not kill the virus. This is because the virus exists in a latent state, the virus will not produce viral proteins or replicate excessively and destroy the host cell (lytic replication). Therefore there are no viral proteins for immune cells to notice and as such the Immune system is not alerted to the presence of the virus. (31) One way in which EBV positive cancers could be treated is to make the Immune system notice the presence of the virus, and in a strange way we do this by causing the virus to replicate more. The idea is that virus will replicate to such an amount that the Immune System will take notice and kill the cells containing the virus, i.e kill the cancer cells. This was the idea behind work by Lee et al (32) where a drug “gemcitabine” which causes the rapid replication of the Epstein-Barr Virus was used in combination with another therapeutic agent to increase killing of EBV cancer cells.

Another way in which we can increase targeted killing of EBV positive tumours is to boost the immune response. One way in which we can do this is to infuse the patient with immune cells that have been made to target EBV positive cancer cells. This was found in another type of cancerous condition that is caused by EBV, called Post Transplant Lymphoproliferative disorder (PTLD). While the name is daunting, this condition is when tumours form after a transplant. Liu et al (33) compared two groups one who had immune cells directed against EBV and one who did not receive this treatment. In the group that had not had the treatment 11.5% of patients developed PTLD in comparison to none of the patients who had received the treatment. (33)

Another way in which we can improve the immune response is to turn off signals that turn the immune system off. It is important to have signals to turn the immune system off when an immune

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**Figure 5: Process of methylation**, in the following diagram, we can see in the top line, how a gene is normally expressed when the promoter region is unmethylated. However the bottom line shows in the presence of a methyl group the gene is not expressed.

(Adopted from http://missinglink.ucsf.edu/im/genes_and_genomes/methylation.html)
response is not needed otherwise we would suffer horrible autoimmune reactions and would die very young.\(^{34}\) PDL-1 is one of the signals that turn the immune system off, a drug (Nivolumumab) that is specifically made to block the function of PDL-1 will activate the immune system and this would be useful in fighting cancers.\(^{35}\) Ansell et al\(^{35}\) use Nivolumumab in the treatment of another cancer associated by EBV (Hodgkin Lymphoma) out of 20 patients who were exposed to the drug, 87% of the patients had some positive response to the drug and 17% were cured of their cancer.\(^{35}\)

### 3.5. Microsatellite Unstable Tumours

#### 3.5.1 Genomic Analysis

This term may require some clarification before we proceed, if we consider the first two words in the name, these tumours have instability in the microsatellite genes. The microsatellite genes are genes that normally repair base errors and insertion/deletion loops. Microsatellite instability normally leads to a hypermutator phenotype where the tumours have many more mutations than most other tumours. The reason for this is that if the genetic defects are not repaired, these will be found in future cells and lead to more and more mutations in the tumours. Examples of genes commonly affected in Microsatellite Unstable tumours include MHL1, MSH1, MSH6 and all of these genes are involved in repairing DNA. This subset of tumours accounts for 22% of all gastric cancers.

#### 3.5.2 Targeted Therapy for Microsatellite Unstable tumours

There is a lot of medical literature on whether certain Microsatellite Unstable tumours are more treatable with certain drugs. One of them is a drug called 5-Fluoracil, in a study looking at Microsatellite unstable tumours in colon cancer, it was found that Microsatellite instable tumours responded better to treatment than those tumours without mutations in the microsatellite genes.\(^{36}\) However several studies that have come after, actually disagree with this saying that there is no specific benefit for Microsatellite Unstable tumours treated with 5-Fluoracil and one even says that there is a negative impact.\(^{37}\)\(^{38}\)

As Microsatellite unstable tumours have many genomic mutations, there are some mutations that occur frequently that can be targeted. One of the ways in which we can treat these tumours is via a mechanism known as synthetic lethality. Synthetic lethality is an almost paradoxical yet highly effective way of curing cancer. The idea is that normally if genes notice any errors in the DNA of a cell, other proteins will work on fixing the DNA error or if this is not possible cause the cell to die (in a process called apoptosis). In microsatellite instable tumours, as there are errors in some of the
genes that are involved in fixing DNA errors, the cancer will accumulate more and more mutations. The cell won’t die as other genes will take over repairing the DNA. However using certain drugs called ‘PARP-Inhibitors’ we can block some of the other pathways that can repair DNA. This causes the cancer cell to die, as the errors in the DNA cannot be fixed (Figure 6). The idea of synthetic lethality has been used to success in many other different forms of cancer and the future looks promising for the use of this targeted therapy in Microsatellite Unstable Tumours. 

3.6 Genomically Stable Gastric Tumours

3.6.1 Genomic Analysis
Genomically stable gastric tumours make up to 20% of gastric cancers, however they are associated with a younger age of presentation with the cancer. Data from the experiments conducted by TCGA found that mutations in two genes; RHOA and ARHGAP are almost exclusively found in Genomically Stable Gastric Tumours. These genes are involved in cell motility and TCGA postulate that this gives rise to how the tumours grow and the lack of cohesion (i.e cells sticking to each other) between the cancer cells. The lack of cohesion is an important marker of cancer and can lead to metastatic spread. However it has also been suggested that the RHOA mutations may not directly lead to cancer but rather indirectly interact with genes to cause cancer.

3.6.2 Targeted therapy.
Unfortunately there are currently no therapies available that can target the mutations in RHOA. However Kakiuchi et al, have found hope and propose regions in the protein produced by RHOA which can be targeted. This may build on research by Shang et al who proposes to design small molecules which will block the function of the mutated RHOA. The mechanism is that by preventing a dysregulation in cell motility, the cancer cells will not spread and therefore be more susceptible to local treatment. Fontana et al state that while there are no current therapeutic targets directed against RHOA, there are other targets such as those against blood supply to new tumours, which may be more effective than current best practice treatment for Genomically Stable Gastric Tumours.

3.7. Chromosomal Instability
3.7.1 Genomic Analysis
The largest subset of gastric cancers are the Chromosomal Instability, set which accounts for up to 50% of the gastric cancers. This type of cancer, as the name suggests is characterised with chromosomal abnormalities, be that the gain/loss of entire chromosomes or parts of chromosomes. Due to this, there are multiple genes that can be found in larger numbers that can be gained or be deleted. Several of these genes are known cancer genes such as EGFR and VEGFR. In any form of cancer certain copies of a gene (called alleles) are mutated, however in Chromosomal Instable tumours when the fragment of chromosome containing the normal allele is lost, the patient will only have one faulty allele at a specific genetic loci, and as such not be able to produce a functional protein. This is known as loss of heterozygosity, and this is a key characteristic of this subset of tumours. Some of the most commonly mutated genes are TPS3 and pRB, these are known cancer genes and tumour suppressor genes. Tp53 is used to note any errors in the genome and stop the cell replicating if it notes an error in the DNA. pRB has a similar function, which is to prevent progression into the cell cycle if there is an error in the DNA. When these genes don’t work, the cancer cell can develop more genetic mutations.
Another type of gene affected in this subset are the Receptor Tyrosine Kinase group. (Figure 7) These genes are involved in cellular growth. A molecule called a Growth Factor will bind to each of the receptors, activating them and bringing them together. Binding of the growth factor activates the protein called the Tyrosine Kinase, these can then activate another protein by the addition of a phosphate group. When a relay protein is activated it will cause the activation of many signalling proteins to affect what genes are expressed. Examples of tyrosine kinase genes that are affected include HER2, EGFR and VEGFR. When these genes became mutated the end result is over expression of genes involved in cellular growth, making the cancer cell have uncontrolled growth which is a defining characteristic of cancer.

3.7.2 Targeted therapy for the Chromosomal Instability subset of Gastric Tumours

HER2 is a common therapeutic target that has been used in Breast Cancer. A similar drug that binds perfectly to HER2 called ‘trastuzumab’ is important in killing gastric cancer cells. Research by a group of scientists led by Dr. Bang, found that when Trastuzumab was added to Chemotherapy used to treat HER2 positive cancer, there was an increase on average of 2.7 months of life. A similar molecule was used in the treatment of HER2 positive breast cancer. While there have been some success with using drugs that match the shape of molecules upregulated in cancer, there has also been failures. Notably a drug that blocked both HER2 and EGFR called ‘lapatinib’ was not found to be effective in the following two studies, except in the case of a small group of patients; those aged under 60 and from Asia.

4 Take home messages
- Gastric Cancer can be divided into 4 subtypes based on their genomic errors.
- The treatment for gastric cancer, can be tailored to the genomic subtype, often with results that are better than the current treatment.
- Some of the targeted therapies used in other cancers may be applicable to gastric cancer, and offer hope to patients in desperate need.
5 References


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