

The Status of Germ Line Gene Therapy: An Analysis from an Islamic Ethical Perspective

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Article Info Volume 82 Page Number: 7341 - 7358 **Publication Issue:** January-February 2020

Abstract

Rapid development in the area of medical technological advancement has become increasingly important. As other medical advancement, human gene therapy trial and application has benefited mankind by successfully addressing a range of human genetics disease at the early stage. This therapy has offered a series of potential and successful treatment which gives new hopes to the patients. Nonetheless, the emergence of new technologies lead to contentious issues among physicians, scientist and Islamic scholar especially when it relates with ethical and religious position. It is believed that the comprehensive framework of medical ethics based on the (Maqasid al-Shariyyah) and (Objectives of the Shariah) and QawaidFiqhiyyah (Islamic Legal msaxim) are the best approach to be adopted to deal with the issues. In view of the above, this paper attempts to analyze the Islamic conceptual framework with special focus on Germline Gene Therapy. This study would begin with highlighting on the scientific procedure and the potential uses of Germline Gene Therapy. The Islamic principles originate from the Qur'anic injunctions and tradition of the Prophet Muhammad (pbuh) shall then systematically assessed. Its position is then analyzed within the comprehensive model of the Maqasid al- Syariyyah and the branches of QawaidFiqhiyyah (Islamic Legal Maxims) to draw the parameters of legislation on Germline Gene Therapy. The existing fatwas (Islamic verdict) from other countries shall then highlighted together with the stance of National Fatwa Council of Malaysia on the issue concerned. This study adopts qualitative method using content and doctrinal analysis approach. This study submits that the Islamic fundamental principles of medical ethics are pertinent to respond and maintain the flexibility to this new biomedical advance trial. It further concludes that Germline Gene Therapy isenot permissible (prohibited) in Islamic doctrine for few justifiable grounds. In Malaysia, Islam has been posits as the official religion as enshrined in Article 3 of the Malaysia Federal Constitution. Therefore, it is essentially important to provide the guidelines by developing a complementary framework of Germline Gene Therapy practices and application derived from Islamic perspective. This study propose that the Maqasid al-Syariyyah should be relied on as an effective approach and comprehensive checklist in addressing bioethical human gene therapy issues. However, the establishment of such framework should in concordance with international ethical on gene therapy as to embrace our holistic Islamic ethics globally.

Article History Article Received: 18 May 2019 **Revised:** 14 July 2019 Accepted: 22 December 2019 Publication: 03 February 2020

Keywords: GermlineGene Therapy, Islamic Principles, Maqasid Syariyyah. Qawaid Fiqhiyyah

1. INTRODUCTION

The goal as embodied in Malaysia National Vision 2020 is to reach developed nation status in 2020 with the main aim is on economic area. It also encompasses and highlights the notion of building a civil society. This will essentially mean the development of biotechnologies industries especially in genetic engineering which enable significant life extension is become priority areas and has been hugely emphasized(Chee Hee Leng, 2000). At present, Malaysia is slowly advancing towards and forging ahead with the Industrial 7341



Revolution 4.0.0f the myriad challenges Malaysia faces today, we must ensure that inclusive development in all sectors i.e economics, politics and social and personal development are equipped to meet with this new wave(Mohd Noor Bin Omar. 2017). Rather, IR 4.0 also emphasize that moral and ethical issues that raises by cuttingedge research in biotechnology industry should properly addressed and being shaped in a responsible method, upholds with essential guiding principles; values, cultures and ethics, tolerance and respect to genuine care and compassion. Hence, it could catalyst and propel us towards sustainable and comprehensive development (Schwab, 2016).

Recently, genome editing for non-heritable applications has become applicable in a clinical trial but limited to only for treating diseases. Human gene therapy practices, for example, is amongst the new scientific landmark treatment that has been conducted worldwide with a series of successful treatment in several genetic and inherited disorders.While thousands of patients have already participated in this technique and procedure, the future for medical practices would be expanded bv adopting this new technique.(Lewis, 2003). Within the European countries, the progressive market of gene therapy products and the successful of its clinical trial demonstrate the safety of this technique to treat previously untreatable diseases.

Current technique seldom referred to as Germline Gene Therapy (GGT) is another viable option treatment which scientifically proven as amechanismin correcting disease-causing nuclear and mitochondrial DNA mutations transmitted to gametes causing monogenic disorders. In most cases, once mutation has been transferred to a child, there are limited treatment options being offered(Don P. Wolf, 2019). Therefore, the GGT has been offered to treat mitochondrial disease. Nevertheless, studies show that this kind of therapy have been surrounded by various ethical, legal and social issues that need to be resolved. Although the legal position of GGT has been

discussed in a wide range of priory literatures, not many works have been done so far that carefully examined the application of human gene therapy from the Our'anic verses. the Prophet Muhammad (pbuh)Sunnahand tradition along with the opinions of some Muslim scholars.Islam encouraged persistently biotechnology advancement which perceived in various sectors medicine, agriculture, be it and food productionbut always gives paramount concerns on ethical aspects to safe guard the needs of Muslim population.

In view of the above, this study seeks to evaluate the position of Germline Gene Therapy from the Islamic perspective. In achieving these, the Islamic rulings provided in the Qur'anic andtradition injunctions of the Prophet Muhammad (pbuh) shall then systematically assessed. To embrace Shari'ah holistic approach in this new medical treatment, a thorough study of the position of Germ Line Gene Therapy shall then analysed within the application of the comprehensive model of the Maqasid al-*Syariyyah* and the branches of *QawaidFiqhiyyah* (Islamic Legal Maxims) to draw the parameters of legislation on Germline Gene Therapy. The existing Islamic legislation, Declaration and Resolution, fatwas (Islamic verdict) in few Islamic countries regarding human gene therapy are then examined. Malaysia position which recognised that the official religion in Malaysia is Islam which become dominant in Malay culture, signify the need to embark on this study thus the stance of NationalFatwa Council of Malaysia on the same issue will then examined. From the above analysis, this study would finally recommend that the formation of Shari'ah Framework governing Human Gene Therapy is needed to ensure such practices do not contrave the shari'ahrulings by emphasizing the basic general principle of "preserving public interest and preventing harm".

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2. HUMAN GERMLINE GENE THERAPY: A PRELIMINARY INSIGHT INTO ITS SCIENTIFIC TECHNIQUE AND POTENTIAL APPLICATION

In general, human gene therapy would best defines as a transfer of nucleic acids to theindividual's somatic cells causing therapeutic effect either through correcting genetic defects or via overexpressing proteins (David & Peebles, 2008; Rubanyi, 2001). El-Aneed (2004)is of the same view emphasizing that gene therapy treatmentis genetically based treatment which introduced genetic materials resulting therapeutic effects or preventive purposes (Karpati & Lochmu, 1997). In essence, human gene therapy technique may occurs in either somatic cells or germ cells. It comprises (Mele, 2012; Anderson, 1985) of two distinguish techniques namely Somatic Cell Gene Therapy and Germ line Gen Therapy.For the purpose of this study, discussion will only focus to Germline Gene Therapy.

purpose of conducting Germline The Gene Therapy may consists of therapeutics as well non-therapeutic. For *therapeutics* as purposes, Germline Gene Therapy involves the reproductive cells which means any modification made to the DNA will be transmitted to the subsequent offspring. Procedurally, DNA will be passed into the reproductive cells (eggs or sperm) which would enable for correction of diseasecausing gene mutations variantfrom being transmitted to the offspring. The parental germinal cells (sperm or eggs) of an adult will be alterated and manipulatedpermitting the high percentage of cells consists in the body(Clark, 2012). Following this, it allows for the newgene to be functioned in each and every cell of the individual's body including her germ line which later on be transferred to the next generations. As a result, this therapy would capable to prevent generations future from suffering the mithocondrial disease.

Amongst notable technique used in Germline Gene Therapy related to mithocondrial

transfer for therapeutics purposes is known as Mithochodrial human *Oocyte* Replacement Therapy (MRT) by way of pro-nuclear transfer technique or Maternal Spindle *Complex* Transfer. This technique which conducted by means of IVF procedure is capable to prevent genetic disorders and mtDNA diseases from being inherited tothe lineage either male or female(Giles, Blanc, Cann, & Wallace, 1980; Zhang et al., 2017)In order to fix the embryos at the first palce, MRT technique coulde be conducted to replace the undesired genes with healthy genes. Mainly, the IVF procedure performed in this technique would involves the mixing of the donor's eggs with the biological mothers eggs. The affected embryo would firstly being isolated and the disfunctional gene causing genetic disease will be removed. A vector consists of a healthy and functional gene is then inserted into the embryo and replacing the faulty gene. As a result, it may increase the chances of the new genes being presents in the sperm or eggs during fertilization and thus, the resulting embryo will

This approach is highly effective to redress and thwart genetic disease and hereditary disorders.Reznichenko, Huyser, & Pepper (2016)discover that the sucessfull research conducted hold promises for the prevention of mtDNA disease through micromanipulation in Assisted Reproductive Technology (ART).Other Germline Gene Therapy may also than that. for *non-therapeutic* purposes conducted commonly known as enhancement genetic engineering which the primary target is to merely 'enhance' and for the 'embelishment' the existing known characteristic and phyical appearance.

free from the disease (Willgoost, 2001).

2.1 Oocyte Mithochodrial Replacement Therapy (MRT) by way of Pronuclear Transfer and Maternal Spindle Transfer Technique

A genetics diseases (disorder caused by a mutation in both mtDNA and Nucleur DNA) often caused severe disability and multi-system diseases which abrupt the nervous system and early death



(Samuels, Wonnapinij, & Chinnery, 2013). It commonly occurred to female carrier caused by primary defects in mithochodrial DNA (mtDNA mutation) inherited exclusively through maternal inheritance (Engelstad et al., 2016) whereas Mendelian genetics are often occured in nuclear DNA mutations. Therefore, it is vital important to prevent such disease from being transmitted(Liu & Chu, 2015). Mitochondrial transfer clinic procedure is recently being actively pursued as the best option (Engelstad et al., 2016; Paull et al., 2012; Samuels, Wonnapinij, & Chinnery, 2013; Tuppen, Blakely, Turnbull, & Taylor, 2010). In most cases, women suffered with mtDNA who wish to have genetically related kids have an either to choose between natural option procreation Pre Genetic Diagnosis (hereinafter referred to as "PGD") which merely available to heteroplasmic women or MRT. Unfortunately, PGD is notcapable in detecting mtDNA because only women with low level of mtDNA mutations in oocytes are suitable to undergo this treatment(Craven et al., 2010; Palacios-González & Medina-Arellano, 2017). Therefore, woman have to turn to donor oocytes as other reproductive option for them in order to have children unaffected for mtDNA desiases. Amongst its established techniques include; Human oocyte mithochodrial replacement therapy (hereinafter referred to as "MRT"Pronuclear, Spindle, Ooplasmic and BlastomereTransfer (Reznichenko et al., 2016; Wolf, Mitalipov, & Mitalipov, 2015; Zhang et al., 2017) which both techniques are conducted via Assisted Reproductive using In Fertilisation (IVF) procedure. Vitro This procedure involves the mixing of eggs from the biological mother with the donor's eggs in which the resulting eggs which contain the healthy mitochondrial will then be fertilised with the sperm of the biological father. This technique only tackle mtDNA disease patients and unambiguously protect offspring of the patients from expressing mitochondrial diseases (Sato et al., 2005). Altough the intending mother would not being genetically related to her child while it invloves the used of donor oocytes, but they are

capable to have their genetically own children (Reznichenko et al., 2016).

The procedures for Maternal Spindle Transferfor example are as follows: The nuclei from both eggs (the intended social mother and donor egg) are removed. Then, the nucleus of the donor egg is replaced with the nucleus of the intended mother's egg. The egg now consists of nuclear DNA from the intended mother and mitochondrial DNA from the egg donor. The IVF are used to extract the intending mother's egg which its cytoplasm contains the unhealthy mitochondria. Then, the chromosome will be transferred into the donor while the chromosome which consists of the unfit mitochondria are being discarded.In another separate procedure, a donated egg is also extracted from (a donor) who has healthy mitochondria and the donor's eggs chromosomes will eliminate. Only healthy mitochondria left in the cytoplasm. As a result, the egg contains nuclear DNA from the mother and the healthy mitochondria from the donor. The egg then be *fertilized* with the sperm from the intended father. Theembryo is free from inherited mitochondrial disease and be implanted into the intending social mother (Palacios-González & Medina-Arellano, 2017; Zhang et al., 2017).

2.2 Enhancement Genetic Engineering

Enhancement Genetic Engineering(Anderson, 1985) is another form of Germline Gene Therapy which aim to 'intensify' some characteristic; for instance, put on an additional growth hormone gene into a normal child ; and Eugenic genetic engineering to modify complex human traits such as personality, mental capacity, character, improve height, transformand modify certain distinctive characteristics such as the colour of one's eyes or hair.and to name a few.

Seemingly, the potential application of germline genetic modifications and interventions overtures the possibility of preventing and decreasing the incidence of certain genetically inherited disease within families especially while screening and selection procedures are ineffective.



Since it influences the earliest stage of human development, irreversible damage deducible to defective genes could be ward off before it takes place. This intervention would disturbed and devastatethe patient's descendants. Beyond therapeutic purposes, the genetic interventions uses might be expanded to also 'enhance' normal human characteristics.

3. HUMAN GERMLINE GENE THERAPY:ETHICAL ISSUES

The development of emerging technologies and lucrative demand in diverse knowledge especially in biomedical field require special scrutinyfrom the Muslim scholars from the Islamic perspective.While the scope and uses of Germline Gene Therapy have become expanded to a wide range of uses, it causes grave attention over the ethical issues and safety concerns onthis technique and application

Wirth, Parker, & Ylä-Herttuala (2013) argue that there are genuine and paramount ethical concerns regarding the patient safety of modifying human germline and its potential effects approaches on offspring (Urnov, Lanphier, Ehlen Haecker, Werner, & Smolenski, 2015). The scholars further highlight on the high risk of causing uncontrolled genetic changes in an individual who undergo this therapy by gene therapy which most likely be transmitted to their future generation. Other than that., adverse effects might occurred on the resultant have developmental embryos and offspring after the mitochondrial transfer.Further, they reach to the same view stressing that current technologies in human embryo genome editing is harmful and unethical as it would cause unpredictable effects to future offspring. Technique which causes heritable human genetic modifications poses serious risks, deleterious and dangerous, with unforeseen negative effects on subsequent generations. Other than that, it gives rise to another ethical concerned when it involves election of only those selected embryos who is free from genetic disorders which will be implanted in the mother's womb. The remaining unhealthy embryos shall normally either be discarded or kept for future use or used for research purposes. Whether this should be regarded as unethical action when it touches human dignity and right of life? Serour (2008) in his argument reveals that the germline manipulation involves genetic alteration of embryos while their cells are still totipotent. The resulting children would have a genetic connection to three parents: namely; mother, father, and the mtDNA donor (Liu & Chu, 2015; Mitalipov & Wolf, 2014).

Following this, another pertinent issue from Islamic point of view is that, whether this kind of procedure is ethically permissible when the unity of sperm and eggs are occurred outside the legal valid marriage. Insight into the procedures, new genetic material being exists into either germ cells (sperm or oocytes) or into zygoteprior fertilization.Conducting this technique may result the creation of embryos via In Vitro *Fertilisation* (*IVF*)where it involves the combination of the abnormal women's eggs (from the valid marriage with the husband) with the healthy donor eggs (from other woman outside legal marriage) and fertilized with the sperm (women's husband) by In Vitro Fertilization..

Meanwhile, since the used of human GermlineGene Therapy has also expanded towards Enhancement Genetic Engineering, it also surrounds with serious ethical issues especially where the aim of conducting this technique is only for non-therapeutic purposes i.e for enhancement of human traits. The motive for this kind of therapy is usually the desire to improve appearance where it involves some sort of manipulation of gene where the insertion of a gene would possibly provide perceived beneficial characteristics (Anderson, 1985; Diehl, 2017). This technique is unjustifiable since it could be exploited for non-therapeutic alterations. The modifications allow individual to freely choose the required physical appearance irrespective whether it purposes to gain health or merely enhance and embellish the genetics populations which unethically acceptable.



4. HUMAN GERMLINE GENE THERAPYFROM THE ISLAMIC PERSPECTIVE

The above paramount ethical issues should from be carefully assessed the Islamic jurisprudential principles and current existing fatwas (Islamic verdict). Muslim scholars profound that the advent of human gene therapy could cause major implication to the society at large. Issues surrounded the above procedures need to be thoroughly evaluated especially from the Islamic Fiqh principles. What would be the Islamic point of view on the position of Human *Germline Gene Therapy which conducting mainly* for therapeutic purposes? Does the argument to avoid heritable genetic disease to futuregeneration is justifiable? How does Islam views and come out with the suitable conclusion on this kind of therapy?

Apparently, Eugenic Enhancement Gene therapyis not justifiable and ethically contravenes the Islamic principles. The use of foetus and embryo solely for human experimentation through eugenic genetic enhancement has obviously contradict the God plan as it manipulated the gene pool. This contravene religious values, laws and ethics as it deprives the human dignity. Allah SWT is the Creator of the world in which all creation should follow God's will and order.Human has been created by Allah in the best manner. He gives man intelligence and creates human as the best creatures. He gives us life, knowledge and five senses thus human is perfect creatures physically and mentally. Allah SWT has repeatedly affirms that:

"We have indeed created humankind in the best of molds"

(Surah al-tin:4)

To further supports the above verse, Allah SWT further insists:

"O mankind, what has deceived you concerning your Lord, the Generous, Who created you, proportioned you, and balanced you?"

(Surah al-Infitar 82: 6-7)

The above Quranic verse indicates that Allah SWT has perfect our creation with specific limbs and perfect body parts. The contentious dilemma raise from enhancement germline gene therapy is due to human dignity. This is seen as altering the life forms and rebelling against the sovereignty of Allah. In other words, human cells, tissues and organs belong to Allah. Accordingly, to change or to alter the existing creation is to change what Allah SWT has created since each creation has been given with its own sifat (attitude). Thus, we are not permitted to make any changes in the human body which is after all (Changing the creation of God) without justifiable grounds. As He is the Almighty, He has established the system and specific guideline and ruling, the cause and effect in this world.

The Qur'an assertively uphold that the universe and all the creatures was created by Allah in an orderly manner. This brings us to fully comprehend the whole existence belongs to the Almighty and also to realize the two interrelated ends namely: the nature of Allah's creation and the legal ownership of human form, intelligence and life (Abdi Omar Shuriye, 2006) .In this regard, Allah is the only one who has the bona fide ownership and the aptitude to create. Limitation has been set by God to the extent of man's involvement in the scheme of created things. Equally essential is that human beings have no capacity to make decision regarding the beginning or ending of life which is reserved to divine sovereign.

Hence, it is remarkable to note that the abovementioned verses confirm that Allah is the best creator, and anything considered eugenic (enhancement) technique and not for medical necessity is forbidden. The emergence of enhancement genetic engineering seems to merely manipulate God's creation and give indication that there some other creators beside Allah. It is forbidden from the Shari' ah perspectiveto modify and alterAllah's creation for instance changing sex either by taking hormones or through surgical intervention, without any justifiable medical grounds. In a related dimension, the Qur'an considers illicit in any changes to the form of



human creation. The word of Allah SWT in another Surah:

"So direct your face toward the religion, inclining to truth. [Adhere to] the fitrah of Allah upon which He has created [all] people. No change should there be in the creation of Allah. That is the correct religion, but most of the people do not know"

(Surah al-Rum 30:30)

Thus, anyconduct that manipulate physical body without anyadvantages are prohibited. Other related Prophetic tradition indirectly opposing the GermlineGene Therapy for enhancement position within Islamic legal ruling could be found in hadith narrated by IbnMas`ud:

"Allah has cursed those women who practice tattooing or get it done for themselves, and those who remove hair from their faces, and those who create spaces between their teeth artificially to look beautiful, such ladies as change the features created by Allah. Why then shall I not curse those whom Allah's Messenger (pbuh) has cursed and who are cursed in Allah's Book too?"

Similarly, it was narrated by 'Abdullah where prophet Muhammad (pbuh) said:

"The Messenger of Allah cursed the woman who tattoos and the one tattooed, the woman who fixed hair extensions and the one who had her hair get extended, the consumer of Riba and the one who pays it, and Al-Muhallil and Al-MuhallalLahu

Enhancement Eugenic Germline Therapy can also be categorized as asthethic procedure which by analogy similar of performing cosmetic surgery. (Nor Azura Ahmad Tarmidzi, Wan Abdul Fattah Wan Ismail, Nalisha Mohamed Ramli, Nadia Halib, & Nur Akilah Abdul Ghaffar, 2019). In the Qur'an, the word of Allah states:

"And surely, I will lead them and will fill them with vain desires, and I will command them so that they will slit the ears of the cattle, and I will command them so that they will alter the creation of Allah. And whosoever taketh Satan for a patron, instead of Allah, shall surely suffer a manifest loss"

(Surah al-Nisa'4: 119)

Even though the hadith of the prophet does not impose direct prohibition upon human attributes alteration at the pre-implantation stage of an embryo, but, impliedly, changes of Allah creation without justifiable medical grounds contradicts His plan thus it is forbidden. Hathout (2006)views that the breakthrough of genetic engineering seems to infringe and violate the distinguished features of genetic uniqueness of living organism. Hence, the application of enhancement germline gene therapy for personal traits embellishment is beyond the limit and against the principles of Shari'ah and therefore prohibited.

4.1 Islamic Verdict (Fatawas) on Human Germline Gene Therapy

The Islamic Jurisprudence (Fiqh) Council of the Organization of Islamic World League of the Organisation of Islamic Countries (OIC) in Makkah Al-Mukaramah in its 10th session, 28 June-3 July 1997 hold a decision allowing the "genetic engineering and cloning on germs, microorganisms, plants, and animals, proved that there are legitimate rules which brings to benefits and prevent harm".

No direct fatwa on human genetic engineering has been issued.

Following this, the Islamic Jurisprudence (Fiqh) Council of the Islamic World League of the Organization of Islamic Countries (OIC) in its 15th session, 31th October in 1998 has carefully outlined in details few relevant guidelines on the genetic engineering (Muslim World League & Islamic Fiqh Council, 1998). The fatwas include;

- 1) The use of genetic engineering for disease prevention, treatment, or amelioration on the condition that do not cause further damage are allowed.
- 2) The use of engineering in evil and criminal use or what is forbidden religiously; forbid using genetic

engineering to change human personality

In Singapore, fatwa decision 22th November 2001 on Human Stem Cell Research by the Bioethics Advisory Committee (BAC) gives way to the application of genetic engineering stressing that it used is limited for *therapeutic purposes*, confers the benefit to the mankind and do not cause harm. The fatwas read as follows:

1) Islam encourages human genome research, genetic engineering and other related fields. Nonetheless, it should be utilized for the of mankind for example for the betterment treatment of disease. The research to be conducted should adhere and within the limitation of Islamic Jurisprudence principles namely; "there should not be any harm and nothing should be done to cause harm" which means: Do not cause harm to one self and to others and not do something that will benefit oneself but will harm or cause difficulty to others".

The above decision is in *parimateria* with another Fatwa issued by European Council for Fatwa and Research (ECFR) in Resolution 10/1 Final Statement, the 10th Ordinary Session in Dublin during the period of 23th Zulqaedah 1423 AH, 19th -26th January, 2003, related to cloning and genetic engineering . The Fatwa only covered on the permissibility to conduct genetic engineering towards "*microbiology, microorganism, plants and animals within the Shariahcontrolling criteria and that would give benefits and prevents evil*"

The decision by ECFR shows that the permissibility to conduct genetic engineering in various fields with necessary filter should be passed as prescribed by the Shari'ah. Similarly, this permissibility extended to therapy using stem cells that functioning in replacing the defective ones with the condition it does not damage and harm to fetous above 40 days of age. The position of human gene therapy respectively have not been decided in further detail.

As far as Malaysian situation is concerned, the position of pre-embryos genetic engineering has been unanimously decided by National Council of Islamic Religious Affairs Malaysia held on 22th February 2005 and Fatwa Committee for the State of Selangor Fatwa in pursuant to *Published by: The Mattingley Publishing Co., Inc.* subsection 48 (6) of the Administration of the Religion of Islam (State of Selangor) Enactment 2003 gazetted on 25th May 2006 in issuing fatwa respectively embedded in (Ruling on Therapeutic Cloning and Stem Cell Research). The provision of fatwa includes amongst others;

(5) "Pre-embryos genetic engineering involving modification of perceived beneficial the characteristics and to enhance known characteristic such as the of hairs colour, increased mental capacity, a tendency to tallness, or specific eye colors including gender selection are strictly forbidden (haram). However, gender selection (Pre-genetic diagnosis) is become permissible if there is high certainty that the gender factor would lead to the genetic disorders or chromosomal abnormalities causing death"

Review of the International Fatwa and National Fatwa council of Malaysia further demonstrates that though no direct term has been used referring to germline gene therapy (Eugenic Enhancement Gene Therapy). However, the Islamic legislation taking a clear stance that conducting genetic engineering with the purpose to modify human personality using pre-embryos genetic engineering the involving modification of perceived beneficial characteristics and to enhance known characteristic hairs colour, increased intelligence, a body height, or specific eye colors including gender selection are not permissible. Thus, it has been made clear that eugenic enhancement gene therapy is forbidden.

Following this, to embrace Shari'ah holistic principles into Human Germline Therapy activities and address its ethical consideration, it is essential to further assesses and interpret the position of human gene from the principles of Fiqh,elucidates each component of *Maqasid Al-Syariyyah* and *Qawa'idFiqhiyyah perspective*. This shall further examine in the next discussion.

4.2 Human Germline Gene Therapyfrom the *Maqasid al-Syariyyah*Perspective

*Maqasid al-shari'ah*is the main Islamic law of al-Syariyyah. Accordingto (Auda, 2008).Maqāsidcontains the purposes, intends and ends behind the Islamic principles. *Maqasid al-Syariyyah* is significant to redress and resolve



current contemporary issues (Al-Raysuni, 2013). It has been categorized into three categories : the dharuriyyah (the essentials), the hajiyyah (the complementariness) and the *tahsinivyah* (the desirables or the embellishments). Dharuriyyahis view as a vital requirement for the spiritual and communities' survival of well-being Thesepurposes are perceived as the foundationto general human welfare of this world generate and the hereafter. Dharuriyyahis where the people will depend upon religion and worldly affairs of the. Failure to preserve will definitely cause to total disruption to religion and worldly affairs as it could lead to mischief. There are five classical goals of Maqasid al-Shari'yyah under *dharuriyyat*(necessity)namelypreservation of religion (ad-din), life (al-nafs), intellect(al-a'ql), progeny and blood linage(al-nasl) and wealth or property (al-mal). Accordingly, the legality of the act is judged based on these five goals (Alkaabba, 2016). As such, the theory of medical ethics in medical research should be conducted in accordance with the underlying framework keeping of five pillars of the Shar'iah laws(Afifi, 2007; Al-Shatibi, 1991; Gatrad & Sheikh, 2001; Khan, 2016). This implies that, although Islam encourages to find a cure for a disease, these principles should be given due attention while conducting medical procedures. Hence to be considered ethical any action must satisfy and achieve one or more of the pillars. Failure to fulfil during the medical procedure shall be deemed unethical. Albar (2007)however specifies that the protection of life,intellect andlineage are those closely related with medicine.

i. Protection of Life (al-Nafs)

The main key goal of *al-syariyyah* is the need for the protection *of life(al-nafs)*(Ibn Ashur, 2006).All necessary mechanisms should be performed to prevent any kind of harmful effect from being occurred.If harms and injuries have been inflicted, it is our responsibility toconduct all possible measures to lessen its negative effects. In the medical aspect, it entails the preservation of health and ward off disease, and restoration of health and to remove ailment (Albar & Pasha, 2015). In this regard, many places in the Quran have repeatedly saying that saving and the sanctity

of life remain as a predominant value in Islam. For example, the following Quranic verse states to the effect that:

"Because of that, We decreed upon the Children of Israel that whoever kills a soul unless for a soul or for corruption [done] in the land - it is as if he had slain mankind entirely. And whoever saves one - it is as if he had saved mankind entirely. And our messengers had certainly come to them with clear proofs. Then indeed many of them, [even] after that, throughout the land, were transgressors".

From the above account, in compliance with this objective, Islam instructs us to undergo treatment to preserve the life and body. Having a healthy life would enable individual Muslim to perform observances and fulfil his duty as a Khalifah . Therefore, conducting Human Germline Gene Therapy via MRT and donour oocytes could be seen a means to protect life because without it, future generation life will be exposed to fatal epidemic.

ii. Protection and Preservation of Progeny (al-nasl)

The next pillar of the *dharuriyyat* within the *Maqasid al-syariyyah* is the protection of lineage (*al-nasl*). The progeny or lineage is a must to be protected and any endangering harm should be considered prohibited. Allah SWT instructs human to form families through legal marriage as this is the only lawful way of having children and maintaining our future descendants. This instruction can be found inthe qur'an for example;

> "And marry the unmarried among you and the righteous among your male slaves and female slaves. If they should be poor, Allah will enrich them from His bounty, and Allah is all-Encompassing and Knowing" (Surah al- Nur 24: 32)

Albar (2007)asserts that the progeny or lineage is a must to be protected and any endangering harm should be avoided and hence considered prohibited. In hisanother study, Albar(2002) also highlights that the risks of consanguinity is



common in many Asian and African countries. He then proposes that to control a wide array of genetic disease from being inherited and to preserve the well-being of descendants, it demands medical contributions by various means which could help to ensure that the children and the descendants grow healthily and free from any genetic diseases. Premarital examination before marriage is essential to detect the disease in that couple who will get married. The patient will be given appropriate explanation on the possible risks and options to treat it during genetic counselling session. Other than that, PGD is another preventive action that could be taken to prevent genetic disease at the early stage from being transmitted by allowing abortion for serious diseases (before attaining120 days from conception) (Albar& Pasha, 2015). Nonetheless, PGD is not successful in detecting mtDNA especially when it involves uncommon mutation and its applicability only confined for those women with low level of mtDNa mutations in oocytes (Craven et al., 2010; Palacios-González & Medina-Arellano, 2017). Therefore, other effective measure via donor oocytes shall be considered as to allow the patient to have children free for mtDNA diseases and thus prevent genetics disease from being transmitted. It is apparent from the above discussion that Germline Gene Therapy is not merely for 'enhancement' but could also be used for' therapeutic purposes'. Further question arises: Should we totally close the door for human germline gene therapy dedicated for therapeutic purposes without considering the benefits it might offer?Do the ethical issues in GermlineGene Therapy should not make it permissible? Or, should we accept the lesser of two evils when compared with the impact of some genetic diseases?

Based on the interview conducted with Prof Dr.ArifSallehRosman, Fatwa fellow (Istinbat Unit), Research Department, Malaysia Fatwa National Committee Council, Malaysia "Personal Communication", Malaysian Islamic Development Department (JAKIM), Putrajaya

(15th November 2018), he prefers to suggest he door of Human Germline Gene Therapy should not totally ban since it has been limited clinical option to avertmtDNA being transferredcausing Mithocondrial disease(originate from mixture of mutant and normal mtDNA)(Samuels et al., 2013) and there is an absent of effective means of pre-selecting embryos with PGD (Mitalipov, Amato, Parry, & Falk, 2014). Prof Dr.Ariffurther opines that the application of Germline Gene Therapy could possibly permissible as in some cases, it could be the only effective preventive therapyto prevent and decrease the incidence of genetically inherited disease from develop which could certainly safe future generations. To such extend, the procedure of treating the genes in the reproductive germ cells (sperm or eggs) to allow for the functional gene to be exist in every cell of the individual's body including his or her germ line which in turns modifying the gametesand transmitted shall be considered. The scholar further adds that if this noveltreatmentis adequately proven to be protected and secured, then it is allowed to use them. The above view seems in line with other priory recent studies highlighting that Pronuclear transfer has been conductedand being considered as best technique to mitigate the transmission of mutant mtDNA from a carrier mother to her child at the gamete or zygote level(Craven et al., 2010; Tachibana et al., 2013; Zhang et al., 2017). Whether this technique is forbidden because it interferes with human individuality and autonomy, the informant further argues this issue should not be question. He argues, it is upon the parents to decide the best for their future children. Applying the concept of wilayah(custody), parents possess full rights and responsibility to their children as long as the children has not attained puberty. While the unborn children are not capable to give their informed consent, parents are the most eligible person to give informed consent on behalf of their children to protect their interest.

Prof Dr.Arif further adds that if the medical practitioner could ascertain that this



therapy capable to repair the disorder-causing mutations from transmitting to next offspring while dysfunctional gene causing genetic disease will be removed by replacing with the healthy functional gene which later on capable to produce future healthy generation free from the disease, then, this technique could be considered. From the above account, it is suggested that there is merit in permitting human germ-line intervention. However, he stresses that obviously this technique is more complex than is predicted. Hence, concern about safety and efficacy should be addressed adequately before permitting it especially when it involves the safety and the risks of uncontrolled genetic changes which might in turn causing harm to the patients and their offspring. This technique should be used sparingly and with further scrutiny. Other scholars have also shared the same view asserting that deriving this cardinal principle from the Islamic doctrine, it offers and promote the prevention of genetic diseases which include chromosomal, multifactorial, mitochondrial, and somatic cell genetic disorders particularly to Muslim population from being inherited to the descendants(Albar & Pasha, 2015).

Given the above view, another ethical concern surrounds MRT technique and procedure is the usage of IVF procedure in gametes or preembryos in the laboratory dish which is far more technically difficult. Particularly, when it involves generating healthy embryos through а combination of mother's egg (genetic diseases carrier) with the donor egg (healthy eggs) via IVF procedure. During the procedure, some of the affected and abnormal embryos will invariably be lost or sacrificed and being discarded while some normal and engineered embryo oocytes or zygotes enabled to grow, carrying the modified human genome, it gives rise to major ethical issue. The procedure and technique involved would lead to mafsadahor darar on future generation. From the Islamic legal perspective, there has been in the Our'an or Sunnah a religious injunction prohibiting the use of donor eggs in IVF procedure. Rather it has been decreed as prohibited by the existing Fatawas (Islamic verdict). The fatawas has prescribed some conditions and requirements that should be followed. Though this technique could ensure that the children and the descendants grow healthily and free from any genetic disease, but the procedure is not legitimate.

Reliance should be made to the Qura'nic injunction and hadith stressing on the importance to have legal marriage in order to protect honour of the lineage (al-nasl). In this conflict, duty to respect the value of human life shall be given precedence over the duty to prevent or alleviate suffering. Thus, it is clear that the position of this procedure is *de vacto* not permitted. From the above account, it is submitted that human Germline Gene Therapy via Human Oocyte Mithochodrial Replacement Therapy by Way of Nuclear Transfer Technique or Spindle-Chromosomal Complex Transfer shall not be justifiable and permissible as it will cause destruction towards progeny (al-nasl) and the protection could not be secured at all. The permissibility of conducting this medical treatment shall only confine when the IVF technique is conducted using legitimate biological mother's eggs and sperm from legal marriage. Any combination and mixing of the abnormal woman's eggs with healthy donor's eggs which later on fertilised with the sperm are strictly prohibited.

4.3 Application of Qawa'idFiqhiyyah (Islamic Legal Maxims)in Human Germline Gene Therapy

Islamic legal Fiqhi principles have been enumerated by Muslim scholars to aid to draw Islamic legislation and regulation. However, it is notable that the regulation cannot be solely on a particular maxim but shall be derived from the Quran, Sunnah and supported by evidence. $Qaw\bar{a}$ *id fiqhiyyah* is define as a body of abstract rules which are originated from the detailed study of fiqh(Mustafa, 2014). These basic methods



enable us to easily understand figh when it could encapsulate under one simple principle. These legal maxims is crucially important in Islamic law, especially the principles shall be used to draw a conclusion based on many rules of fiqh(Laldin, 2014). This implies that in the absence of clear injunction in the Quran and hadith, the application of Qawa'idFighiyyah (methods of figh) plays a significant role. Hence, it shall be accustomed in tandem with the problem for people's benefits and attain(Magasid al-Shari'yyah). As emphasized by (Al-Ageel, 2010)anumber of basic jurisprudential principles (Figh principles) could be taken into consideration in deliberating the status of contemporary medical treatment and therapy while there have no absolute rulling could be found in the Quran and the Sunnah.

Those principles are relatively promotes attaining ends, and abstaining evil, e.g., when removal of harm is followed by an after-effect harm, a lesser degree of two harms should be prevail. Further to that, the doctrine of *maslahah* (benefit or interest) as suggested by IbnAshur (2006) is to uphold good and confers benefits and refuted the evil .This implies that doctrine of *maslahah* (benefit or interest) is predominantly the most established jurisprudential principles that could be invoked in relation to medical treatment so as to *Human Germline Gene Therapy*. Hence, this study further suggests the application of the relevant Islamic fiqhPrinciplesin each different procedure of Germline Gene Therapy Therapy.

4.3.1 *Matters are determined according to their intentions (Al-Umur bi-maqasidiha).*

This maxim originates from the Hadith: Umar ibn al-Khattab reported: The Messenger of Allah, peace and blessings be upon him, said, "Verily, deeds are only with intentions. Verily, every person will have only what they intended" (SahihBukhari, Kitab al-Iman, No:54). This general maxim agreed upon by Islamic scholars because of its consistency and relevance toIslamic fiqh.The whole sphere of fiqh is concerned with rules or judgments on matters. Any action or matter $(um\bar{u}r)$, whether physical or verbal, should be considered and judged according to the intentions (niyyat) of the (wrong) doer. Any action made for or against should be in conformity with the intention of the offender(s) involved in the case. Rather, intention is the supreme basis of for the practice'sacceptability. If it is correctly conducted with regard to its method, but have incorrect intention, then Allah SWT would not accept (Nor Azura, 2019). This implies that human actions/deed will be judged according with his intention, and thereby the ruling (al-hukm) will also be decided in accordance with his intention.

Thee meaning of this maxim according to 'Abd Al-Karim Zaydan (2015)is that, ruling of the Shari'ah and all human daily life shall be judged according to the doer's intention behind the acts at the time of the implementation. However, the same action may cause a different ruling when it is executed with dissimilar intention. Therefore, Islamic permissibility or non-permissibility should be based on the above authentic source.

a) Oocyte Mithochodrial Replacement Therapy (MRT) by way of Nuclear Transfer Technique and Maternal Spindle Transfer

The maxim (*Al-Umur bi-maqasidiha*) is essentially pertinent as a reference in ascertaining the need for conducting Germline Gene Therapy by means of MRT technique shall then permitted. Within this context, if the intention and the purpose is to remove genetic diseases and disorder from being inherited to future offspring and restore function then, MRT can be done. This objective is in line with the figh rules: *every harm and distress should be eliminated*.

Therefore, as noted above, MRT technique via *Maternal Spindle transfer* and *Pronucleur transfer* if performed with the purpose of preventing Mithochondrial disease affected by mtDNA mutation from being inherited to the next generation, then, it shall be allowed according to Islamic perspective.



b) Eugenic Enhancement Gene Therapy

Otherwise if Germline Gene Therapy is conducted for the purpose of genetic enhancement and with the intention to change the destiny prescribed by Allah SWT and to achieve purely embellishment rather than for therapeutic purpose, thenit is forbidden. Such act is impermissible where the procedure is done towards the eggs and sperm with the intention to gain enhancement (in terms of intellectual capacity and physical enhancement) to the descendants. Furthermore, if the intention (niyyah) is just to tamper with the human body, to improve and enhance the patient's features on a purely aesthetic level without an extreme and real needs and beyond that what Allah SWT has plan, then such therapy and treatment are completely forbidden. This act is considered as changing Allah's creation which is the essential factor why human genetic enhancement gene therapy should not be allowed. The intention behind these kinds of genetic enhancement is just seeking beautification, which does not stand alone as a cogent reason for justifying them. As indicated by this first maxim; al- umuru bi-maqasidiha, it is unlawful for the Muslim physician to carry out such treatment to merely improve and enhance their appearance which heritable and affected their future descendants.

4.3.2 Harm must be eliminated (*Al-Dararyuzalu*)

This maxim rooted from a renownedhadith Prophet Muhammad (pbuh) "La dararwaladirar(¥ ضرر ولا ضرار) "Let there be no infliction of harm or its reciprocation". Based on this hadith, Dharar means inflict more substantial to harm/injury/damage to others absolutely. i.e. injury not to begin with. Ibn al-Athir said in his book al-Nihayah: La dharar means: A person should not cause harm to others, so that reducing some of his rights. While Dhirar means retaliatethe harm with harm. A person should not cause any kind of harm to another person in order to reciprocate the harm he has caused. This means

that it is not proper for someone to cause harm on others, or his property, whether to begin or to retaliate it(Ibn Al-Athir, 2011). Dharar has also been used in the Our'an to describe instances of considerable harm such as the distress caused by serious illness(Ibn Nujaym, 1980).These include the following verse which says: "Deal not unjustly, and ye shall not be dealt with unjustly" (Surah al-bagarah 2: 279). In a nutshell, this maxim is primarily intended to repel and protect Conversely, this maxim closely from evils. related with *non-maleficence* principle upholding the concept of avoiding the risk of harm to others with the aim to balance between the benefit with the harm. Two branches of principles to describe Germline Gene Therapy, namely Al-DaruratTubihu Al-Mahzurat (dire necessity renders the impermissible to be permissible) comeunder the main principle of *al-dhararyuzal*, Major Muslim Scholars in particular the four Mazhab allow a dire necessity that threatens a core objective of the Islamic to overturn a normative prohibition, Al-Darurat Tuqaddaru Biqadariha (emergency measured according to the need).

a) Oocyte Mithochodrial Replacement Therapy (MRT) by way of Nuclear Transfer Technique and Maternal Spindle Transfer

In assessing the dangerous situation or distress (*darurah*) principle, the level of shallcarefully emergency examined.Germline Gene Therapy generated numerous discussions on whether it should be done, and whether the potential benefits outweigh the harmmay arise. Although Mitochondrial diseases are individually mostly quite infrequent but, they can have serious consequences. These serious consequences include chromosomal. multifactorial, mitochondrial disease which could be inherited to future generation. Moreover, with the recent new technique of genome editing, namely the RISPR/Cas 9.Germline interventions hasexpanded since the procedure could be used for disease prevention (Rubeis & Steger, 2018). This new technique brings possible life-saving therapy and



holds out the prospect of real cures for a number of their diseases, this maxim is amongst the best argument for the supporters of Germline Gene Therapy procedure via MRT to allow this technique to be conducted. The benefits of conducting in terms of saving future generations from being inherited with Mitochondrial diseasehave been shown to outweigh any side effect of MRT procedure in Germline Gene Therapy.

From another perspective, other relevant maximcould highly possibly rely uponwhile performing MRT technique and procedure namely 'avoidance of harm takes priority over the attainment of some benefit. It takes priority over an act with a comparable benefits, prohibits conducting any medical procedure, if there is an absolute harm predominantly which outweighs benefits ('Abd Al-KarimZaydan 2015). Applying this maxim, any risks or harms associated with this kind of technique shall be removed. There would be unpredictableeffects of Germline Genewhich severe risks might have been occurred. Although the technique would cures the disease, other additional mutations might possibly be exist and will be transmitted on to the subsequent offspring.. Interms of safety, there exist a risk of uncontrolled genetic changes, its potential benefits offered might potentially be outweighed by the risks involved. This implies that the potential harms of conducting of Oocyte Mithochodrial Replacement Therapy (MRT) outweigh its potential benefits due to the ethical, technical and practical limitations. In the event where there exist a collusion between the harm and the benefit, refuting the harm is to be prevail since it is vital compared to implementing the command. Thus, the concept of avoiding harm is so important as stated in the Qur'an:

"Because of that, We decreed upon the Children of Israel that whoever kills a soul unless for a soul or for corruption [done] in the land - it is as if he had slain mankind entirel (Surah al-Maidah 5: 32)

Other branches of maxim underAl-Dararyuzaluread as al-Akhdh bi akhaff al-Dararayn(Lesser darar takes precedence over greater darar) which means that when there is a clash of two harmful situations and we are to choose either of the two, we have to choose the lesser of the harmful situations No medical treatment and therapy is performed without any risk and side effect. MRT technique is still considered involved unpredictable risks and harm. However, the Shari'ah does consider the positive aspect of MRT via Maternal Spindle Transfer and Pronucleur Transfer. From the medical perspective, this technique offers many advantages to those suffering with genetic disease. Applying this maxim least harm of the two dangerous things are allowed to be occurred from the Islamic figh principle to ensure individual is free from any genetic defects post mitochondrial Hence, if the transfer complication and consequence would become more severe if surgery is not performed as compared to the complications of the technique, then, the relevant maxim would be "Irtikabuakhaffu al-dhararain" which is "do the least harm of the two dangerous things" (Al-Zarqa, 1989).

The applicable rule if there is a clash between an individual harmand a societies harm is "Inflicting darar on individual is tolerated in order to abstainmore general harm on the society'(Yutahammalu al-darar al- khass lidafa' al-darar al 'aam)This means when two harmful situations clash, then choose the more general one. This occurred while when two harmful situations collide, one involving an individual or a handful of individuals and the other involves a whole community, in this situation, we must avoid the harmful situation involving the whole community although this may harm one or more individuals. In the MRT technique and procedure of Germline Gene Therapy, although post technique of Mithocondrial therapy mightsometime cause harm to future generation, it must still be administered because the consequence of the harm, if not



administered, would be greater. The harm that befalls an individual would be much less serious compared to the harm in the form of a genetic disease that could remain dormant in individual's reproductive cells and being transmitted to the subsequent offspring which endangers their life.

a) Eugenic Enhancement Gene therapy

Analysis from the above maxim, it shall further submit that conducting Enhancement Eugenic GermlineGene Therapy for purely cosmetic uses and enhancement goal is excluded any application to enhance beyond the normal range such as to aptitude taller, stronger, or to be more intelligent.

The ethical concerns raises from Enhancement genetic engineering cannot justify on the ground of preventive medicine. This principle has been made clear that Islam prohibits human to alter, modify and intervene with the Allah SWT actual plan. Though this alternative modern technique must be praised and saluted since it is scientifically proven to treat a range of genetic disease, however, the expansion of their application put in conflict with Islamic principles in some situations particularly with regard to Enhancement Eugenic Germline Gene Therapy. This kind of therapy falls under tahsinivvat (embellishment) tho which can bring human life perfection.Tahsiniyyah towards is the desirability's toachieve refinement in people's customs and conduct.According to Al-Shatibi (1920)Tahsiniyyah is to achieve better utilization, and the simplification of *daruriyyah* and *hajiyyah*. If this is being neglected, it does not bring hardship to the normal people's lifebut it merely lead to discomfort of life.According to (Al-Ghazali, 1937)tahsiniyah shall not be considered to be an argument in deriving for Shari'ah rulings unless there is evidence. In the context of Enhancement Eugenic Germline Gene Therapy experimentation for the purpose of refinements may not be considered at all if there is any risk. The same view as in (Hathout, 2006) when the scholar stresses that utilizing gene therapy

technique via genetic engineering other than to combat illness, is not justifiable. The maxim under discussion has provided the basis of numerous other maxims on the subject of *darar*. Similarly, many rules stem from this maxim such as ward off iniurv. This means"*public* public interest overrides the individual interest" The reason lies is that Islamic law tends to protect and preserve public interest rather than private notwithstanding some injury and harm might inflict on such individual (private). Thus, if the intent for such prohibition of enhancement eugenic germline gene therapy is to save and protect the public from future harms by an individual, then it may be permitted

Concluding Remarks

The above discussion clearly implies different types of Human Germline Gene Therapy would produce to the different position and judgement. It is clear that in Germline Gene Therapy, safety and efficacy are major challenge.Under certain conditions, Human Germline Gene Therapy should only focus on the therapeutic application and it shall be permissible for only medical purpose. However, it shall only be made applicable for humans once the safety and efficacy issues are resolve and being tested. Strict and stringent ethical guidelines are required to prevent any misuse of the technology. The practice shall be permissible provided the procedure and technique are carried out in line with the stringent conditions provided by Islamic ruling. The 5 principles goals and of Magasid al-Shariah's framework as well as the concept of preventing harm takes precedence over securing benefitare among the guiding principles that should be relied upon while assessing the permissibility. It has brought to surface several other Islamic Legal Maxims such as aldararyuzal, IrtikabAkhaf Al-Dhararain and al-Umurbimagasidihathat either support or oppose its implementation. In conclusion, the legal position of Human Germline Gene Therapy technique application and via Oocvte Mithochodrial Replacement Therapy (MRT) by



way of Nuclear Transfer Technique and Maternal Spindle Transfer should be assessed by taking into consideration the above Islamic comprehensive principles. Nonetheless, considering that its major technique involves mixing of sperm and eggs (intended mother and donor eggs) outside legal marriage using IVF procedure, this procedure shall de facto forbidden.On the other hand, this study further concludes that Germline Gene Therapy via Eugenic Genetic Enhancement is notpermittedin Islam because of the unjustifiable intended purpose. The objective of Shari'ah and Islamic legal maxim are important Guidelines in the formation of law in Malaysia by virtue of especiallyArticle 3 of Malaysia Constitution. Further research is needed in order to integrate religious perspective into the contemporary medical treatment and research.

Acknowledgement

The authors would like to extend deepest appreciation to the Dean of the Academy Of Studies Contemporary Islamic (ACIS), UniversitiTeknologi MARA. Shah Alam, Selangor, Malaysia Prof. Dr. Hj. MuhamadRahimi Osman, and specifically the UniversitiTeknologi MARA (UiTM) for their financial support to the author in attending and presenting this paper at this 23rd World Conference on Applied Science, Engineering And Technology 24th - 25th October -2019 || Melbourne, Australia.

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