How Controversy and Socioeconomic Factors Influence Stem Cell Research

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Abstract: Adult stem cells dominate worldwide stem cell clinical trials. We investigated factors that may explain levels of stem cell research across different countries. Stem cell trials from clinicaltrials.gov were counted and categorized based on the country, the type of stem cell used, and whether that type is ethically controversial. The trial data were compared with characteristics of the countries such as population and GDP. We looked at the general ethical position of the countries by ranking their favorability toward abortion via their legislation. We found GDP, which may be indicative of the interest and means a nation can put toward research, to be the most predictive measure of stem cell use. No correlation was found with national abortion legislation, which is an indicator of ethical positions on life issues in a country. Thus, it would seem that the use of stem cells, namely the significantly greater use of adult stem cells over other more controversial types, is likely to be more influenced by their scientific utility and not by other social or ethical opinions. In addition, ESC and other ethically controversial research does not appear to be necessary for the US to dominate worldwide stem cell research.

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Introduction

Stem cells have the ability to self-renew and differentiate.[1] Self-renewal means that a cell has the capacity to make copies of itself. Differentiation means that the cells can turn into other types of cells. Major categories of stem cells include adult stem cells (ASCs),[2] cancer stem cells (CSCs),[3] embryonic stem cells (ESCs),[4] perinatal stem cells (PSCs),[5] fetal stem cells (FSCs),[6] and induced pluripotent stem cells (iPSCs).[7] ESCs, PSCs, and iPSCs have a differentiation ability called pluripotency which means that a single cell of this type can become any cell type in the adult human body.[8] ASCs and FSCs are usually multipotent which means that a single source of these cells can only differentiate into a few different cell types.[9]

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[1] Gilbert, SF. 2014. *Developmental Biology*. Sunderland, MA: Sinauer Associates, Inc, 320; Alberts, B, A Johnson, J Lewis, M Raff, K Roberts, and P Walter. 2002. *Molecular Biology of the Cell*. 4: 401. New York: Garland Science; Wolpert, Lewis, Cheryll Tickle, T Jessell, P Lawrence, E Meyerowitz, E Robertson, and J Smith. 2011. *Principles of Development*. Oxford: Oxford University Press, 600; Schoenwolf, GC, SB Bleyl, PR Brauer, and PH Francis-West. 2009. *Larsen's Human Embryology*. Philadelphia: Elsevier, 162; Wilt, FH, and SC Hake. 2004. *Principles of Developmental Biology* New York: W.W. Norton & Company, 18; National Institute of Health. 2001. "The Adult Stem Cell." Stem Cell Information. 2001; Carlson, BM. 2009. *Human Embryology and Developmental Biology*. Philadelphia: Mosby, 54.

[2] Dulak, Józef, Krzysztof Szade, Agata Szade, Witold Nowak, and Alicja Józkowicz. 2015. "Adult Stem Cells: Hopes and Hypes of Regenerative Medicine." *Acta Biochimica Polonica* 62 (3): 329–37. https://doi.org/10.18388/abp.2015_1023.

[3] Wang, Tao, Sarah Shigdar, Michael P. Gantier, Yingchun Hou, Li Wang, Yong Li, Hadi Al Shamaileh, et al. 2015. "Cancer Stem Cell Targeted Therapy: Progress amid Controversies." *Oncotarget* 6 (42):

[4] Damdimopoulou, Pauliina, Sergey Rodin, Sonya Stenfelt, Liselotte Antonsson, Karl Tryggvason, and Outi Hovatta. 2016. "Human Embryonic Stem Cells." *Best Practice and Research: Clinical Obstetrics and Gynaecology* 31: 2–12. https://doi.org/10.1016/j.bpobgyn.2015.08.010.

[5] Antoniadou, Eleni, and Anna L. David. 2016. "Placental Stem Cells." *Best Practice and Research: Clinical Obstetrics and Gynaecology* 31: 13–29. https://doi.org/10.1016/j.bpobgyn.2015.08.014; Can, Alp, and Sercin Karahuseyinoglu. 2007. "Concise Review: Human Umbilical Cord Stroma with Regard to the Source of Fetus-Derived Stem Cells." *Stem Cells* 25 (11): 2886–95. https://doi.org/10.1634/stemcells.2007-0417; Couto, Pedro S, Alexey Bersenev, and Frances Verter. 2017. "The First Decade of Advanced Cell Therapy Clinical Trials Using Perinatal Cells (2005 – 2015)." *Regenerative Medicine* 12 (8): 953–68;

[6] Soubelli, Valentina, Pascale V. Guillot, and Paolo De Coppi. 2016. "Induced Pluripotent Stem (IPS) Cells from Human Fetal Stem Cells." *Best Practice & Research Clinical Obstetrics & Gynaecology* 31 (June): 112–20. https://doi.org/10.1016/j.bpobgyn.2015.08.007; Götherström, Cecilia. 2016. "Human Foetal Mesenchymal Stem Cells." *Best Practice and Research: Clinical Obstetrics and Gynaecology* 31: 82–87. https://doi.org/10.1016/j.bpobgyn.2015.11.010.

[7] Hirschi, KK, S Li, and K Roy. 2013. "Induced Pluripotent Stem Cells for Regenerative Medicine" 6 (8): 277–94. https://doi.org/10.1021/nn300902w.Release.

[8] Redfield, EE. et al. 2021. "Types of Stem Cells Used in US-Based Clinical Trials Between 1999 and 2014." Catholic Social Science Review. 26:175.

[9] Redfield. 2021. 174.

ESC and FSC research are ethically and politically controversial because they involve the destruction of human organisms at an embryonic or fetal stage of development.[10] Despite predictions of ESC research's promise in prestigious journals[11] and support from research institutes and nonprofit organizations, ESCs have had little success in producing clinical trials or treatments.[12] Instead, clinical trials are dominated by ASCs[13] and the only stem cell treatments that have received FDA approval are with adult stem cells.[14] Some argue that the lack of ESC and FSC success is due to the ethical controversy of human ESCs and FSCs.[15] Perhaps political concerns related to their ethically controversial nature have hindered treatments and clinical trials. In contrast, treatments and clinical trials with less controversial stem cells such as ASCs might be inflated due to their less controversial nature. On the other hand, ESCs and FSCs may be used in few clinical trials and treatments because they are just less useful scientifically.

The purpose of this study is to analyze factors that may influence the types of stem cells used in clinical trials worldwide. We investigated various social and economic factors across countries to see whether they could be used to predict the number or distribution of stem cell clinical trials. Factors analyzed

[10] While FSCs are normally controversial, they could be obtained after a miscarriage which would not be controversial. However, the authors are not aware of any published examples of FSCs derived in this way. In addition, the non-controversial stem cell types could be derived in controversial ways. For example, iPSCs could be derived from tissue obtained after an abortion. ASCs, iPSCs, and PSCs are categorized as widely accepted here because they are commonly derived in an ethical way and are not controversial when derived ethically.

[11] The journal *Stem Cells* published an article in 2010 on their position statement on hESC research. In this statement, *Stem Cells* commended FDA's approval of use of hESCs in clinical trials for spinal cord injury treatment. Regarding the development of iPSCs in clinical trials, *Stem Cells* stated that iPSCs should be "compared with the gold standard of hESC at every step of experimentation." Stojkovic M, Pittenger MF, Nolta JA, Lako M, Lappin TR, Murphy MJ Jr. Stem Cells' position statement on hESC research. Stem Cells. 2010 Sep;28(9):1A. doi: 10.1002/stem.517. PMID: 20809560. https://doi.org/10.1002/stem.517; In *Nature*, Dr. Dieter Egli, acclaimed professor of Colombia University, predicted that embryonic stem cell research would "lead to unprecedented discoveries that will transform life." Cyranoski, David. 2018. "How human embryonic stem cells sparked a revolution." *Nature* (555):428-430. https://www.nature.com/articles/d41586-018-03268-4

[12] Redfield. 2021. 161-191.

[13] Redfield. 2021. 169-191.

[14] Prentice, D & Tarne, G. (2007) Treating Diseases with Adult Stem Cells. *Science Magazine,* 1-16. https://www.science.org/doi/10.1126/science.315.5810.328b

[15] Baumgartner, Fritz. 2019. "Human Embryonic Stem Cell Research, Abortion, and Publication Bias in the New England Journal of Medicine." *The Linacre Quarterly*. 86 (1):103-114 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6537346/; Boonstra, Heather D. 2016. "Fetal Tissue Research: A Weapon and a Casualty in the War Against Abortion." Guttmacher Institute. https://www.guttmacher.org/gpr/2016/fetal-tissue-research-weapon-and-casualty-war-against-abortion

were a country's gross domestic product (GDP), GDP per capita, population, and abortion legislation. A correlation between a country's stem cell clinical trials and its abortion legislation may suggest that the stem cell research in a country is being affected by ethical perspectives since abortion and embryonic stem cell research are undeniably linked.[16] If a correlation between a country's stem cell clinical trials and other factors such as GDP, GDP per capita, and/or population is found, it would suggest that ethical biases/perspectives are not the major influence in stem cell research and thus stem cell research choices would be more likely to be due to scientific utility. While previous studies have examined the treatments and uses of stem cells in clinical trials,[17] we are not aware of any studies that examine clinical trials across countries and the potential influences on the types of stem cell clinical trials conducted.

Methods

Clinical trials involving stem cells were categorized based on the country where the stem cell research was conducted and the type of stem cell used. Countries were categorized by GDP, population, and favorability to abortion.

Data Collection

Studies involving the use of stem cells between 1999 and 2014 that were registered on 'https://clinicaltrials.gov' were found, according to previous methods.[18] Briefly, we searched the term(s) "stem cell," "umbilical cord blood," "Wharton's jelly," "perinatal," "perinatal cell," and "perinatal stem cell." We also searched the term "stem cell" in the World Health Organization database and

[16] Jensen, David A. 2008. "Abortion, embryonic stem cell research, and waste." *Theor Med Bioeth.* 29(1):27-41

[17] Desai, Amar, Yan Yan, and Stanton L Gerson. 2018. "Concise Reviews: Cancer Stem Cell Targeted Therapies: Toward Clinical Success." *Stem Cells Translational Medicine* 34: 1–7. https://doi.org/10.1002/sctm.18-0123;

Hovatta, Outi, Sergey Rodin, Liselotte Antonsson, and Karl Tryggvason. 2014. "Concise Review: Animal Substance-Free Human Embryonic Stem Cells Aiming at Clinical Applications." *Stem Cells Translational Medicine* 3 (11): 1269–74;

Jackson, Wesley M, Leon J Nesti, and Rocky S Tuan. 2012. "Concise Review: Clinical Translation of Wound Healing Therapies Based on Mesenchymal Stem Cells." *Stem Cells Translational Medicine* 1 (1): 44–50;

Ilic, Dusko, Liani Devito, Cristian Miere, and Stefano Codognotto. 2015. "Human Embryonic and Induced Pluripotent Stem Cells in Clinical Trials." *British Medical Bulletin* 116: 19–27. https://doi.org/10.1093/bmb/ldv045;

Couto, Pedro S, Alexey Bersenev, and Frances Verter. 2017. "The First Decade of Advanced Cell Therapy Clinical Trials Using Perinatal Cells (2005 – 2015)." *Regenerative Medicine* 12 (8): 953–68;

Trounson, Alan, and Courtney Mcdonald. 2015. "Review Stem Cell Therapies in Clinical Trials : Progress and Challenges." *Stem Cell* 17 (1): 11–22. https://doi.org/10.1016/j.stem.2015.06.007; Li, Matthew D, Harold Atkins, and Tania Bubela. 2014. "The Global Landscape of Stem Cell Clinical Trials" 9 (1): 27–39 https://pubmed.ncbi.nlm.nih.gov/24236476/;

[18] Redfield. 2021. 169-191.

found that all of the 969 clinical trials that resulted were either already in our data (963) or did not meet our criteria (6).

The stem cells used in the trials were classified as one of six types. Stem cells taken from the inner cell mass of a blastocyst, which is an organism at an embryonic level of development, were classified as ESCs.[19] Cells derived from harvested fetal tissue such as aborted fetuses were FSCs.[20] Cells that were reprogrammed to become pluripotent, immortal cells were iPSCs.[21] Cells acquired from an individual after birth were ASCs.[22] Cells taken from extrafetal membranes such as the placenta, umbilical cord, and amniotic sac at the time of birth were PSCs.[23] Cells derived from cancerous tissue were CSCs.[24]

```
import openpyxl
import requests
from bs4 import BeautifulSoup
print("Make sure that the excel file you are using is put in the same folder location as this program\n")
print("I also suggest using a copy of whatever file you are using since this program will write over any
existing cell data if you choose a column with data already in it\n\n")
print("It should take the program about 0.6 seconds per study to retrieve the country information\n\n\n")
excelSheet = input("Excel file name:      ") + ".xlsx"
print("\n\n")
countryColumn = input("Enter the letter of the Column that you would like the country put in:      ")
print("\n\n")
column = countryColumn.upper()
wb = openpyxl.load_workbook(excelSheet)
sheet = wb['Sheet1']
count = 0
for row in sheet:
    count +=1
    cell = str('A' + str(count))
    cellValue = sheet[cell].value
    print(count)
    country = ""
    if count >1:
        URL = "https://clinicaltrials.gov/ct2/show/" + cellValue + "?term=" + cellValue + "&draw=2&rank=1"
        page = requests.get(URL).text
        soup = BeautifulSoup(page, 'lxml')
        this=soup.findAll('td', class_='ct-header3')
        text = str(this)
        list1 = text.split("</td>")
        countryList=[]
        for item in list1:
            if "padding-top:2ex" in item:
                newList = item.split(">")
                location = newList[1]
                newerList = location.split(",")
                country = newerList[0]
            if country not in countryList:
                countryList.append(country)
        countryListAsString =""
        thisCount = 0
        for country in countryList:
            if thisCount >0:
                countryListAsString += ", "
            countryListAsString += country
            thisCount += 1
        cell = str(column + str(count))
        sheet[cell] = countryListAsString
wb.save(excelSheet)
print("\n\n          ALL DATA HAS BEEN SAVED TO FILE\n\n\n\n")
input("          CLOSE PROGRAM")
```

Figure 1. Program written in python to determine location of clinical trials.

[19] Damdimopoulou. 2016.
[20] Soubelli. 2016. 112-20.
[21] Hirschi. 2013. 277-94. Soubelli. 2016. 112-20
[22] Dulak. 2015. 329-37.
[23] Soubelli. 2016. 112-20.
[24] Wang. 2015.

The country in which each trial was carried out was determined from the registry with a program written in python (Fig. 1). If multiple countries were listed for a trial, it was counted as a separate trial for each country involved, thus the total number of trial counts seen in Table 2 (5574), is higher than the actual number of registered trials (4287) used in our analysis. If a clinical trial employed stem cells that matched with multiple categories, it was recorded as falling under all applicable categories. Trials listed separately for Czechia and the Czech Republic were merged under Czech Republic. The countries Algeria, Lebanon, South Africa, Cayman Islands, Hong Kong, Taiwan, and Puerto Rico were removed from the data set. Those countries either did not have proper trial listings, did not have abortion information, or had jurisdictional and sovereignty questions. In total, 63 countries were included in our analysis after these exclusions (Table 1).

Table 1. Countries used in analysis, organized by continent. 63 total countries were included in the analysis.

North America	Colombia	Austria	Greece	Belarus	**Asia**	Malaysia
United States	Peru	Switzerland	Portugal	Lithuania	China	Saudi Arabia
Canada	**Europe**	Sweden	Ireland	Luxembourg	Korea	Indonesia
Mexico	Germany	Denmark	Slovakia	Serbia	Israel	Jordan
Jamaica	France	Poland	Croatia	Iceland	India	Philippines
South America	Italy	Czech Republic	Slovenia	Latvia	Iran	Vietnam
Brazil	Spain	Russian Federation	Bulgaria	Uruguay	Singapore	**Oceania**
Argentina	United Kingdom	Norway	Romania	**Africa**	Turkey	Australia
Panama	Belgium	Finland	Estonia	Egypt	Japan	New Zealand
Chile	Netherlands	Hungary	Ukraine	Tunisia	Thailand	

Studies that did not involve the usage of stem cells or progenitor cells were also excluded from this study. For example, clinical trials that involved the usage of cells from the stems of plants (i.e. "plant-stem cells") were excluded. When a clinical trial indicated the involvement of "stem cells", it was classified according to the subtype of stem cells used which are adult, embryonic, fetal, perinatal, induced pluripotent, and cancer stem cells. Clinical trials that did not mention "stem cells", but did mention "progenitor cells", were merged with the appropriate stem cell category. A trial was included if it involved the administration of stem cells, improved the usage of stem cells, or derived stem cells for a potential treatment, even if they were not the main intervention. A trial was not included if it did not administer, isolate, or examine stem cells even if it potentially altered a patient's stem cells (see NCT01167166 for example) or only examined patients who had previously received stem cells. If stem cells were mentioned in a trial, but there was no indication of the type of stem

cell used, it was classified as using stem cells, but no particular subtype was assigned.

Table 2. Counts of trials by stem cell type used for countries with five most total trials in analysis and counts of trials for all countries used in analysis.

	Adult	Embryonic	Extraembryonic	Embryo Proper	Induced Pluripotent	Cancer	Total
United States	2354	4	173	1	18	45	2604
Germany	275	0	5	0	0	4	284
France	227	1	10	0	3	3	244
China	171	0	54	0	0	7	232
Italy	191	2	11	0	0	3	207
Total Trial Counts for 64 Countries	5062	12	360	2	27	111	5574

A system to rank the favorability of countries to abortion was developed. The legal status of abortion in different countries was determined using data from the Population Division of the United Nations Department of Economic and Social affairs for the year 2013[25] (unpopulation.org). We chose 2013 as the year to represent abortion policy as this was the most recent year that had data available within the timeframe of our dataset (1999-2013) and the majority of the clinical trials occurred in the latter half of the timeframe.

We determined the number of countries with each abortion law and ranked the laws from the least common to most common. A weighted rating was created for each law and we normalized the ratings so that they would add up to 100. If a law allowing abortion was found in many countries, such as allowing abortion for the life of the mother, it was given a lower rating. In one country abortion was not allowed for any reason and this rating was set at zero. If a law allowing abortion was found in fewer countries, such as allowing abortion on demand, it was given a higher rating. Initial ratings were calculated by the following equation:

$$\frac{\text{total countries} - \text{no. of countries allowing abortion for that reason}}{\text{total no. of countries}} \times 100$$

After the initial ratings were determined, final ratings were calculated by normalizing the initial ratings so that they added up to a maximum rating of 100.

[25] United Nations. 2013. "World Abortion Policies 2013." Department of Economic and Social Affairs Population Division. https://www.un.org/en/development/desa/population/publications/pdf/policy/WorldAbortionPolicies2013/WorldAbortionPolicies2013_WallChart.pdf

Table 3. Number of countries where abortion is allowed for a particular reason along with associated abortion favorability ratings.

Legal grounds on which abortion is permitted United Nations - Department of Economic and Social Affairs - Population Division (2013)								
Abortion Allowed for	**None**	**Life of Mother**	**For Woman's Physical Health**	**For Woman's Mental Health**	**Rape/ Incest**	**Fetal Impairment**	**Economic or Social**	**On Demand**
Countries	1	62	55	53	51	48	41	36
Initial Rating	0	1.56	12.70	19.64	24.53	31.37	45.83	64.29
Normalized Rating	0	0.78	6.35	9.83	12.27	15.69	22.93	32.16

Population and GDP data from 2013 for each country was taken from the World Bank Group[26] and used to calculate GDP per capita for each country. ASCs, PSCs, iPSCs, and CSCs were characterized as "widely accepted" while ESCs and FSCs were characterized as "controversial." We used data from 2013 in order to match the timeframe of our clinical trial dataset.

Statistical Analysis

The dependent variable in our analysis was the number of stem cell clinical trials and the independent variables were the following: GDP, GDP per capita, abortion rank, and population. Both linear and multiple regression analyses were run to examine the correlations between these variables. A standardized residuals outlier test was run on the linear regressions in Microsoft Excel, with outliers removed if $r_i > 3$. Each linear regression is analyzed for outliers independent of the other regressions. For the multiple regressions, variables with significant p-values ($p < 0.05$) were identified and a second regression analysis was conducted only for those variables (GDP and population). Multiple regression equations were created from the coefficients of the intercept, GDP, and Population.

A χ^2 test of association was used to determine whether abortion legislation, GDP, GDP per capita, and/or population were associated with the number of stem cell clinical trials. For this test, GDP was grouped into tiers according to methods used by Pew Research.[27] The first tier goes up to two-thirds the median GDP, the middle tier being two-thirds to two times the median, and the upper tier being two times the median and above. The countries were grouped

[26] data.worldbank.org

[27] Bennet, Jesse; Fry, Richard; Kochhar, Rakesh. 2020. Are You in the American Middle Class? *Pew Research Center*. https://www.pewresearch.org/fact-tank/2020/07/23/are-you-in-the-american-middle-class/

by population in a similar manner and the three tiers run against the sums of trials of each type of stem cell. Lastly, countries were grouped by GDP per capita into the three tiers and the χ^2 test was run with the counts of each type of stem cell trial for each tier. Significance was assessed at $p < 0.05$.

Results

The highest correlation with abortion rank is seen where abortion rank explains 8.48% of CSC trials (Fig. 2D). Abortion rank explains 2.22% of ASC trials (2B), 1.80% of PSC trials (2C), 0.30% of iPSC trials (2E), and 0.42% of ESC trials (2F).

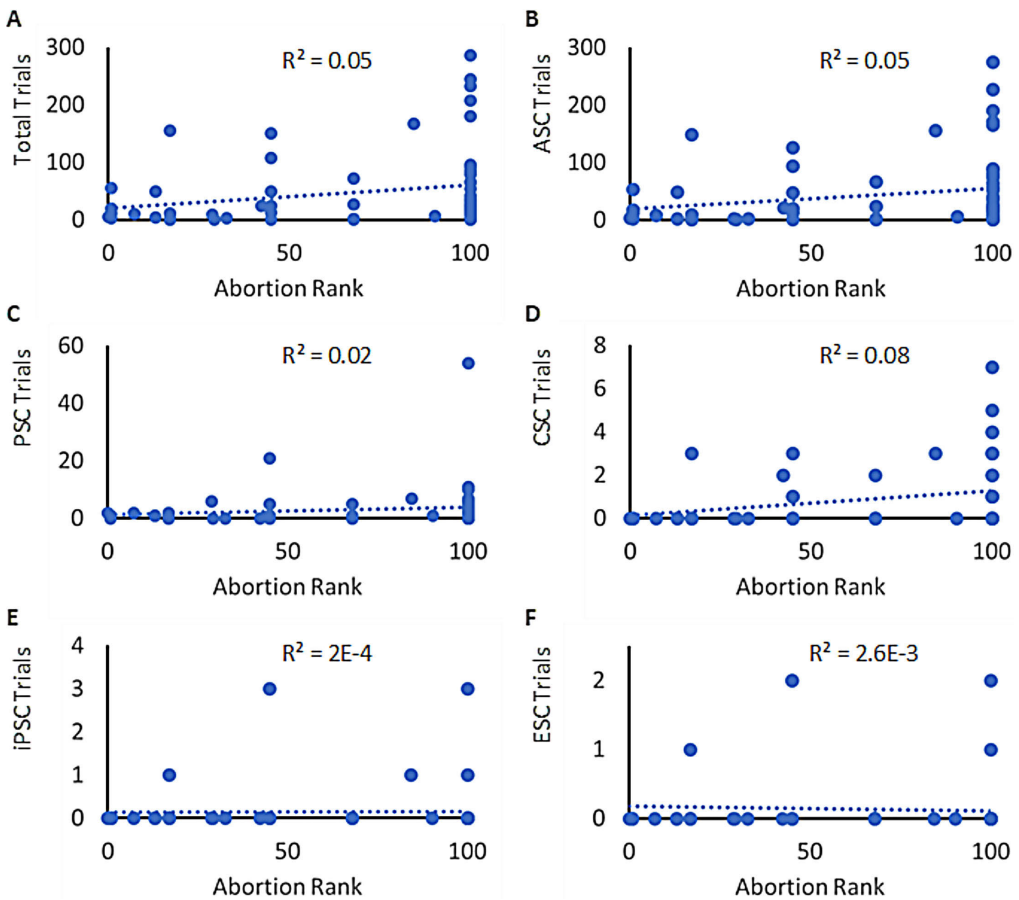

Figure 2. Stem Cell Clinical Trials vs Abortion Rank. A) Total stem cells B) Adult stem cells (ASC) C) Perinatal (PSC) D) Cancer (CSC) E) Induced pluripotent (iPSC) F) Embryonic (ESC). Each coordinate represents a particular country. Fetal stem cells are not included because no clinical trials remain when outliers are removed from that graph using the standardized residuals test.

There is a relatively low correlation between GDP per capita and number of stem cell clinical trials across countries. GDP per capita has the highest correlation with CSC trials at 19% (3D). GDP per capita explains 9.3% of ASC trials (3B), 2.0% of iPSC cell trials (3E), 1.0% of ESC trials (3F), and 0.050% of the PSC trials (3C).

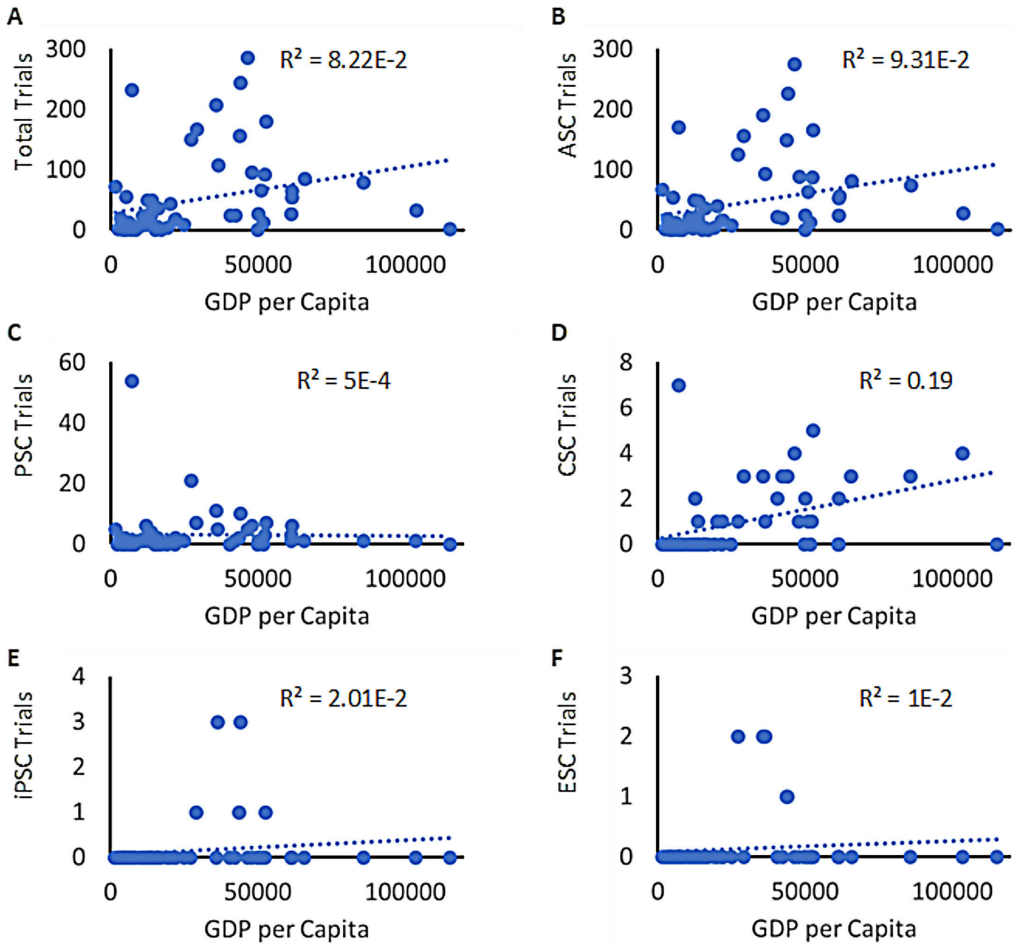

Figure 3. Stem Cell Clinical Trials vs GDP per Capita. A) Total stem cells B) Adult stem cells (ASC) C) Perinatal (PSC) D) Cancer (CSC) E) Induced pluripotent (iPSC) F) Embryonic (ESC). Each coordinate represents a particular country. Fetal stem cells are not included because there are no clinical trials when outliers are removed from that graph using the standardized residuals test.

There is a relatively high correlation between GDP and the number of stem cell clinical trials. The highest correlation is seen with GDP explaining 82.2% of ESC (Fig. 4F). GDP also explains a large percentage of PSC trials at

70.7% (4C), 67.5% of ASC trials (4B), and 64.2%, of FSC trials (4G). GDP explains a much lower percentage of CSC trials at 28.4% (4D) and only 6.38% of iPSC trials (4E).

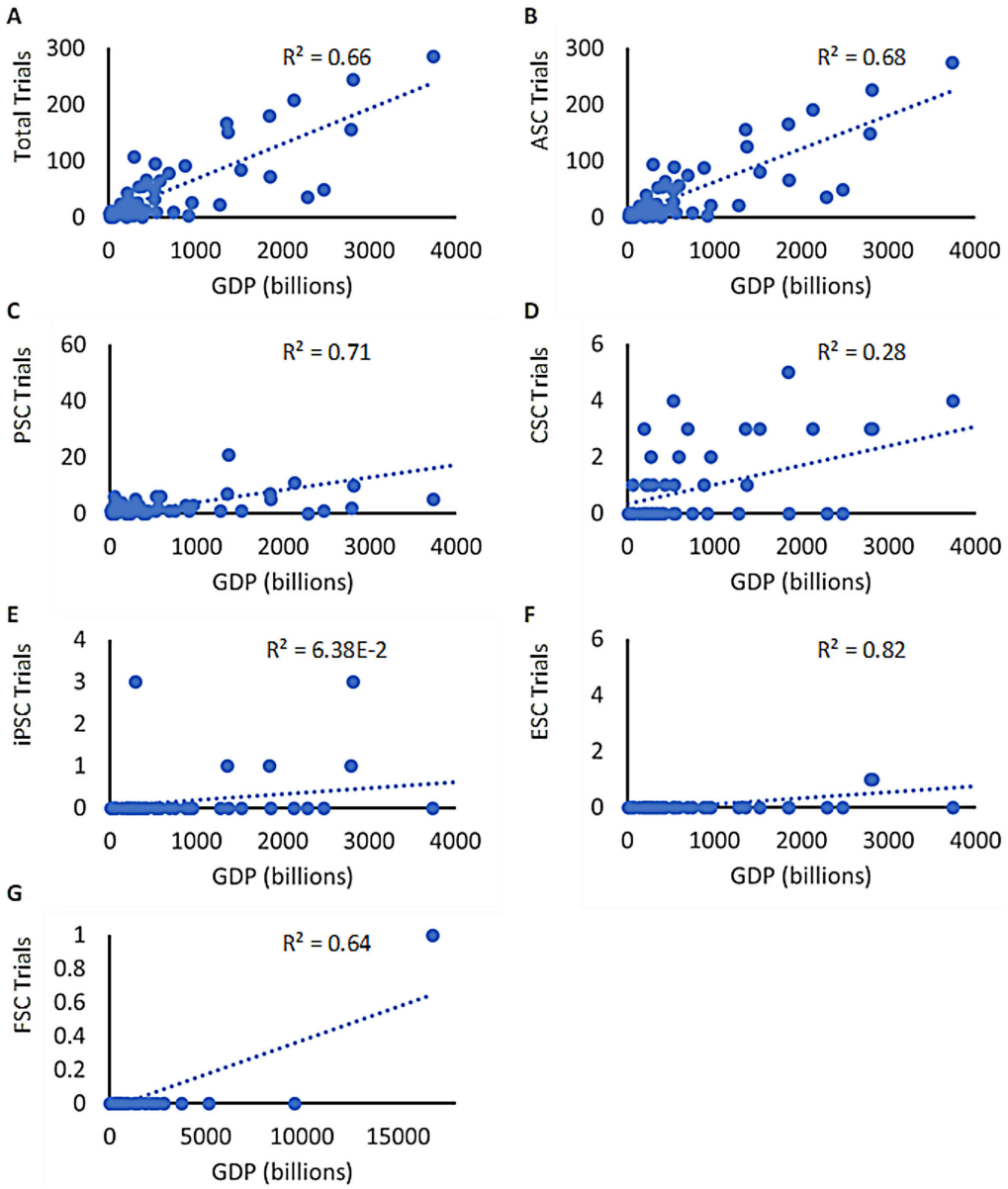

Figure 4. Stem Cell Clinical Trials vs GDP. A) Total stem cell trials B) Adult stem cells (ASC) C) Perinatal (PSC) D) Cancer (CSC) E) Induced Pluripotent (iPSC) F) Embryonic (ESC) G) Fetal (FSC). Each coordinate represents a particular country.

Population predicted less than 15% of clinical trials in four of the five stem cell types. PSCs stand out with the highest correlation at 47.5% (Fig. 5C). CSCs and ASCs have similar correlations, as population explains 10.1% of CSC trials (5D) and 5.75% of ASC trials (5B). ESC and iPSC clinical trials have very low correlations with population at 0.170% (5F) and 0.19% (5E) respectively.

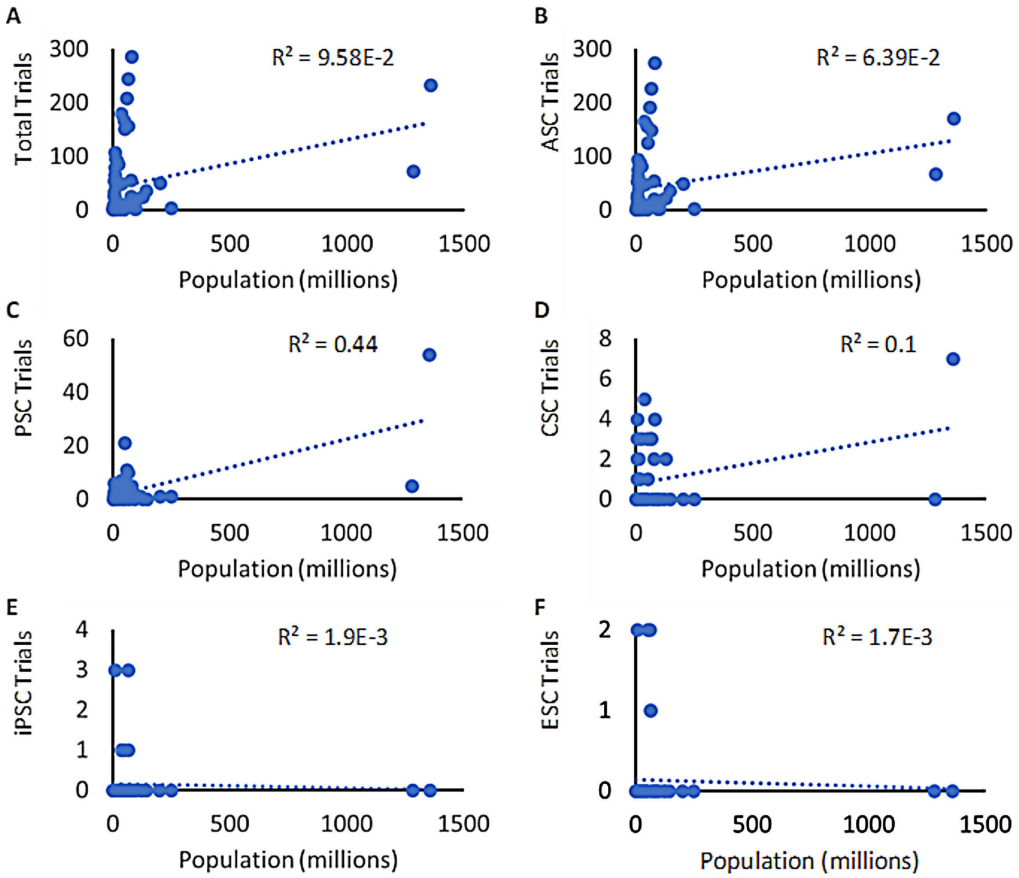

Figure 5. Stem Cell Clinical Trials vs Population. A) Total stem cell trials B) Adult stem cells (ASC) C) Perinatal (PSC) D) Cancer (CSC) E) Induced Pluripotent (iPSC) F) Embryonic (ESC). Each coordinate represents a particular country. Fetal stem cells are not included because no clinical trials remained when outliers are removed from that graph using the standardized residuals test.

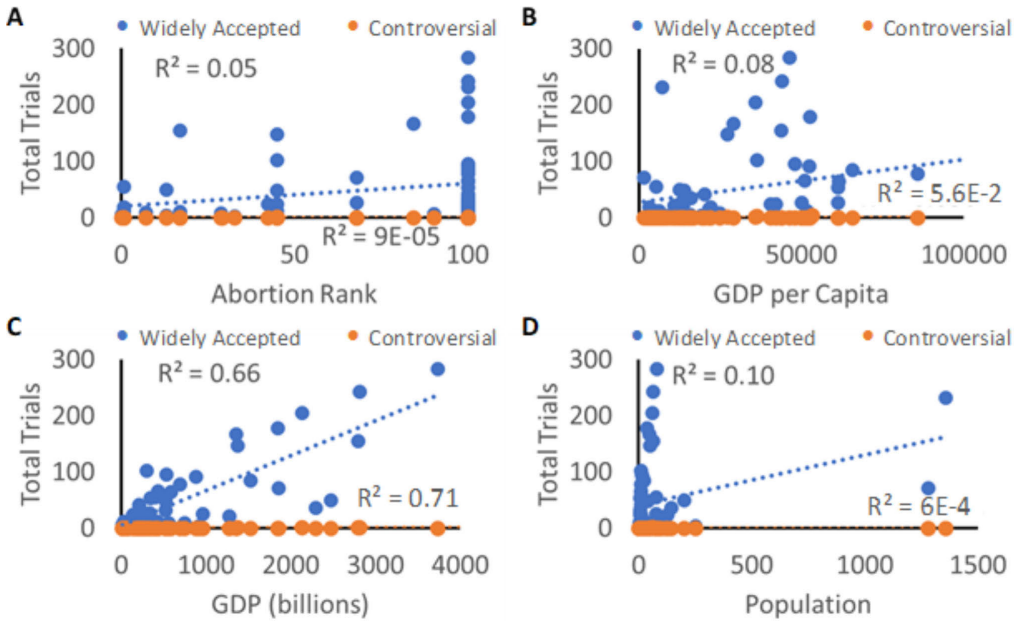

Figure 6. Clinical Trials Grouped as "Widely Accepted" or "Controversial" compared to predictive factors. A) Abortion Rank B) GDP per Capita C) GDP D) population.

Trials of widely accepted stem cells (ASCs, CSCs, PSCs, and iPSCs) and controversial stem cells (ESCs and FSCs), follow similar patterns of correlation with the three independent variables. Both show low correlations with GDP per capita, predicting only 8.28% of widely accepted trials and 5.6% of controversial trials (Fig. 6B). Population also had little predictivity, with 9.69% for widely accepted trials and 0.06% for controversial trials (6D). Likewise, Abortion rank shows low correlation at 5% for widely accepted and 9E-3% for controversial (6A). GDP, however, continues to exhibit high correlation with 66.38% for widely accepted and 70.49% for controversial (6C).

The multiple regression test is used to determine which variables have statistical significance when tested as a group. GDP and population are the only dependent variables that result in a significant p-value when in regressions with clinical stem cell trials.

For each multiple regression equation for the different stem cell trials, the GDP coefficients all have positive values (Table 5). This indicates the direct relationship between GDP and stem cell trials. The population coefficients all have negative values in the multiple regression equations, indicating the inverse relationship between population and stem cell trials (Table 5). ASC clinical trials display coefficients with the highest absolute values, meaning that GDP and population have the strongest effect on ASC clinical trials (Table 5).

Table 4. Multiple regression p-values of stem cell trial types with GDP and population across countries. The variables abortion rank and GDP per capita were not included in the final multiple regression model because they did not have a significant p-value when in initial multiple regression analysis and were thus excluded from the final models.

p-values	GDP	Population
Adult	5.91E-24	1.1E-06
Perinatal	5.56E-24	9.9E-03
Cancer	5.57E-25	1.1E-06
Induced Pluripotent	2.6E-19	4.1E-06
Embryonic	1.23E-10	1.8E-03
Fetal	4.49E-07	2.4E-02
Total Trials	3.47E-24	1.7E-06
Controversial	3.43E-24	1.8E-06
Widely Accepted	9.13E-11	1.7E-3

Table 5. Multiple regression equations of stem cell trial types with GDP and population across countries. y = number of stem cell trials.

Stem Cell Trial Type	Multiple regression equations
Adult	y = -20.99 + 0.12*GDP - 0.43*Pop
Perinatal	y = -3.01 + 8.92E-03*GDP - 1.54E-2*Pop
Cancer	y = -0.63 + 2.83E-03*GDP - 9.50E-03*Pop
Induced Pluripotent	y = -0.28 + 9.16E-04*GDP - 3.79E-03*Pop
Embryonic	y = 0.02.75E-2 + 2.18E-04*GDP - 9.82E-04*Pop
Fetal	y = -4.61E-03 + 4.80E-05*GDP - 2.11E-04*Pop
Total Trials	y = -24.88 + 0.14 * GDP + -0.46*Pop
Controversial	y = 0.02.29E-2 + 2.6E-04*GDP - 1.19E-03*Pop
Widely Accepted	y = -24.90 + 0.13*GDP - 0.46*Pop

FSC clinical trials had coefficients with the smallest magnitude, meaning that GDP and population have the weakest effect on clinical trials with FSCs. (Table 5).

All regressions with abortion rank as the dependent variable had correlations below 5%. GDP per capita explains 4.79% of abortion rank (Fig. 7C), GDP explains 1.59% of abortion rank (Fig. 7A), and population explains nearly 0% of abortion rank (R^2 = 3E-05, Fig. 7B).

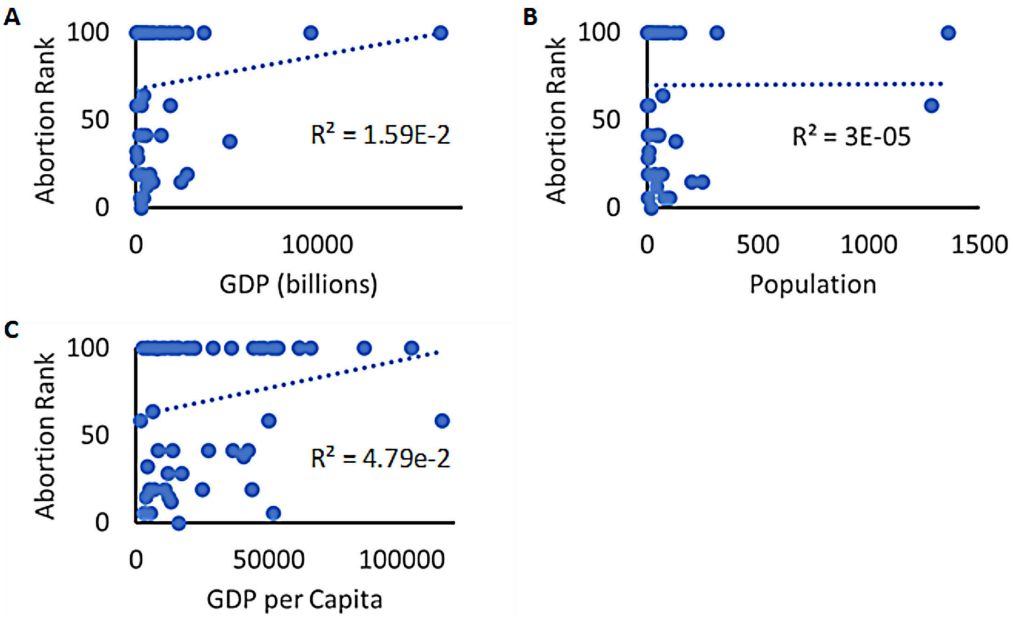

Figure 7. Collinearity between abortion rank and other factors. A) GDP, B) population, or C) GDP per capita.

Abortion rank does not exhibit a significant relationship with any of the other predictive factors, including GDP which is the best predictor of stem cell use. In all of the regressions, the United States was an outlier most frequently (80% of all singular and multiple regressions) due to the country's stem clinical trials exceeding all other countries by a significant amount. While the United States was the most common outlier, other notable outlier countries were Israel (20%), China (15%), and Japan (10%). No other countries were an outlier in more than one regression.

Table 6. χ^2 test of association. The trial type refers to the type of stem cell clinical trials conducted (i.e. ASC, CSC, ESC, FSC, iPSC, or PSC). The trial controversy variable contains two levels: widely accepted stem cell types (includes ASC, CSC, iPSC, and PSC clinical trials added together) and controversial stem cell types (includes ESCs and FSCs).

	A) Trial Type vs GDP	B) Trial Type vs GDP per Capita of Country	C) Trial Type vs Population of Country	D) Trial Type vs Abortion Policy	E) Trial Controversy vs Abortion Policy
p-value	0.23	2.78E-11	0.24	1.00	0.93

χ^2 tests of association revealed that the type of clinical trials a country undertakes are not significantly affected by GDP, population, or abortion policy (Table 6). GDP per capita did show a significant association with the types of stem cell clinical trials ($p = 2.78E\text{-}11$). Individual values from χ^2 calculations indicate this significance is due to PSC use (Table 7). If PSCs in the first tier of GDP per capita are excluded, there is no significant association between GDP per capita and stem cell type. The χ^2 test showed no association between the types of stem cell clinical trials and abortion policies. Similarly, abortion policies did not affect whether a country conducted clinical trials that are ethically controversial or widely accepted trials. If US data is excluded, there is no change in statistical significance.

Table 7. χ^2 results for each category in trial types vs GDP per capita. The calculated χ^2 value for PSC trials of the 1st GDP per capita division is significantly higher than all others. The first tier contains countries in the lowest third of GDP per capita. The third tier contains countries in the highest third of GDP per capita.

GDP per capita tiers	ASC	ESC	PSC	FSC	iPSC	CSC
1st	2.901	0.96	53.93	0.16	2.15	0.38
2nd	02.98E-3	0.76	0.48	0.12	1.63	0.44
3rd	0.254	0.27	5.85	4.57E-2	0.62	0.13

Discussion

In this study we grouped worldwide stem cell clinical trial data according to the country and type of stem cell used. Socioeconomic factors of the countries were compared with the clinical trial data to understand how these factors influence the use of stem cells in clinical trials. Most countries in our study had relatively permissive abortion laws (Table 3). For example, 36 of the 63 countries allowed abortion for all the circumstances laid out by the United Nations as of 2013. Only eight countries allow abortion in fewer than three of the

circumstances we evaluated, and Chile is the only country to not permit abortion under any circumstance. It is notable that the range of abortion favorability of the analyzed countries is relatively small compared to the numbers of stem cell clinical trials conducted. The abortion rank range for most countries is 17 to 100 (half of them being 100); while clinical trial counts, not including the United States (2620) ranges from 1 to 286 with more even distribution. With abortion favorability as an indicator of the ethical positions of the country, it seems that most countries have similar abortion ethics even though they have very different levels of stem cell research.

Abortion favorability and population were poor predictors of clinical trial numbers and the types of stem cells chosen for research (Figs. 2 & 5 and Table 6D & 6C).). These results suggest that neither population, nor ethical controversy over abortion affect stem cell research choices. PSCs are an exception as they have a relatively high correlation with population (R^2=0.44). One potential explanation for the relatively high correlation between perinatal stem cells and population is that since perinatal stem cells are typically acquired from extraembryonic tissues after birth, countries with more births (higher population) would produce more stem cells for this research. However, the correlation seems to be largely due to just one data point (China) that when removed completely changes the trendline and drops the R^2 to 1.2E-2. Therefore, the high correlation is more likely to be an artifact and does not appear to be reflective of trends across all countries.

GDP per capita was also generally a poor predictor of clinical trial numbers (Fig. 3) indicating that relative prosperity of a country's people (GDP per capita) does not influence the amount of stem cell clinical research. However, the χ^2 test indicates that GDP per capita does influence which types of clinical trials are chosen with countries with a low GDP per capita disproportionately choosing perinatal stem cell research (Table 6B). However, this χ^2 result is an artifact caused by China. Despite the second highest GDP, China's immense population yields a very low GDP per capita; but the number of clinical trials performed by China do not fit with the other countries in the lowest GDP per capita bracket. If China is excluded from the χ^2 test, GDP per capita does not influence which types of clinical trials are chosen.

GDP was the best predictor of clinical trial numbers with most regressions having an R^2 over 0.6 (Fig. 4). While higher GDP generally promotes greater numbers of stem cell clinical trials, the χ^2 analysis indicates that GDP does not affect which stem cell types are chosen for clinical trials (Table 6A). Even though ESC clinical trials were most correlated with GDP, according to the multiple regression equations the GDP coefficient (slope) was much higher with ASCs (0.12) than with ESCs (2e-4). This demonstrates that for a given increase in GDP, more ASC clinical trials will be generated than ESC clinical trials. These results show that for a given amount of money, countries across

the world invest more in ASC research than ESC research, suggesting a worldwide recognition of the greater usefulness of ASCs compared to ESCs and all other stem cell types.

Both the controversial and widely accepted stem cells had relatively high correlations with GDP (R^2=0.66, R^2=0.71, Fig 6.). Groupings based on controversy showed no notable association with abortion favorability (Fig. 6A) suggesting that preexisting ethical views do not encourage or discourage particular types of stem cell research. The significant predictivity of GDP suggests again that choices are driven by economics and not by ethics or controversy.

The United States by far surpasses all other countries in the number of stem cell clinical trials. A few other countries such as Israel (20%), China (15%), and Japan (10%) were found as outliers semi-regularly but the United States was removed from nearly all comparisons (80%) because it produces such a disproportionate share of stem cell clinical trials. These results suggest that concerns that 'the United States will fall behind in stem cell research if ESC research is not supported', are unfounded.[28] The dominance of the United States in stem cell research is mostly driven by ASCs and research with ESCs contributes very little to clinical trials in the US or any other nation.

While the ratio of controversial to widely accepted stem cell trials changes slightly (0.25% to 0.30%) when the United States is removed, the number of adult stem cell trials (2708) still significantly outnumbers all other types with perinatal being the next highest (187). Given that the United States so greatly surpasses other countries in trial counts as well as GDP, a more detailed analysis of the United States, perhaps comparing the same factors for individual states may provide a better picture of factors that influence stem cell research and whether interstate trends match trends seen throughout the world.

Conclusion

Similar to other studies,[29] this study used data that is a few years older than the publication date due to the time it takes to compile and analyze the data. While we rated abortion favorability in a country based on the reasons that abortion was legally acceptable, abortion favorability could also be estimated in other ways such as gestational age limits or public polling. Another limit of our study is that we used one year to represent abortion policy (2013) while our

[28] Ford, Liz. *Us 'falling behind' in stem cell research*. The Guardian. 6/1/2006. https://www.theguardian.com/science/2006/jun/01/highereducation.usnews; Conte, Marisa L. et al. *Globalization and changing trends of biomedical research output*. JCL Insight. 6/15/2017. https://insight.jci.org/articles/view/95206

[29] Coleman, Prisilla K. et. al. 2012. "Reproductive history patterns and long-term mortality rates: a Danish, population-based record linkage study." *European Journal of Public Health*. 24(4):569-574.; Raymond, Elizabeth G. and David A. Grimes. "The comparative safety of legal induced abortion and childbirth in the United States." *Obstetrics & Gynecology*. 119(2): 215-219.

clinical trial data spans a number of years (1999-2014). However, there are few differences in abortion legislation over the timeframe of the study and most of the clinical trials occur in later years of the study. Therefore, using one year to represent abortion legislation is not likely to significantly change results or conclusions. Future studies that explore other ways to estimate abortion attitudes could help to confirm our findings.

A likely explanation of our results is that ASCs are indeed more scientifically meritorious and so the more prosperous countries will be apt to conduct greater amounts of trials involving those types. Our results indicate that the significant discrepancy in the use of ASCs versus all other types is not a result of any controversy or biases but is likely to be representative of what is most useful. Advantages of ASCs include multipotency, lack of tumor formation, being well tolerated by the recipient's immune system, lack of ethical controversy and popular support.[30] Multipotency potentially decreases differentiation toward undesired cell types. The popular support and lack of controversy allows potential treatments to be acceptable to the maximum number of potential patients and thus may be a more profitable investment for a company. These key advantages are likely to be the reason why ASCs dominate clinical trials. In addition, because there are many different types of multipotent ASCs it is possible to potentially get any cell type needed by choosing the correct ASC for the particular application even without pluripotency. PSCs probably have the second highest number of clinical trials because they are the only stem cell type besides ASCs that don't form tumors, and are well tolerated by the recipient's immune system.[31] However, their pluripotency may be a disadvantage compared to ASCs, as PSCs[32] ESCs, iPSCs, and FSCs probably have fewer clinical trials because ESCs and iPSCs have the disadvantage of teratoma formation, ESCs and FSCs are generally rejected by the patient's immune system, and all three of these stem cells types have the disadvantage of tumor formation.[33]

In addition, ESC and other ethically controversial research does not appear to be necessary for the US to dominate worldwide stem cell research. Future studies that explore other ways to gauge scientific utility or abortion attitudes could help to confirm that the dominance of noncontroversial stem cells in clinical trials are due to their greater scientific merit.

[30] Redfield. 2021. 174.
[31] Ibid, 175.
[32] Ibid.
[33] Ibid.