Nos. 14-1418, 14-1453, 14-1505, 15-35, 15-105, 15-119, & 15-191

In The Supreme Court of the United States

DAVID A. ZUBIK, et al.,

Petitioners,

v.

SYLVIA BURWELL, et al.,

Respondents.

On Writs Of Certiorari To The United States Courts Of Appeals For The Third, Fifth, Tenth And D.C. Circuits

BRIEF *AMICUS CURIAE* OF THE BREAST CANCER PREVENTION INSTITUTE IN SUPPORT OF LITTLE SISTERS OF THE POOR HOME FOR THE AGED, DENVER, CO, ET AL.

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QUESTION PRESENTED

Whether the HHS Mandate that violates the free exercise rights of non-profit organizations fails to "further" the asserted compelling interest in promoting women's "preventive" healthcare because the Government selectively ignored widely-accepted research showing that certain contraceptive drugs significantly increase risks of breast, cervical and liver cancer, as well as research showing significantly increased risks of other serious diseases, including HIV, stroke and heart attack.

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STATEMENT OF INTEREST[1]

Breast Cancer Prevention Institute ("BCPI") is a non-profit corporation that educates healthcare professionals and the general public through research publications, lectures, and internet resources about ways to reduce the surge in breast cancer incidence attributable to avoidable risks. BCPI is directed by Angela Lanfranchi, M.D., F.A.C.S., a breast surgeon and graduate of the Georgetown School of Medicine (M.D. 1975).

BCPI has an interest in showing that the HHS Mandate's burdens on the Petitioners' religious beliefs cannot be justified under Religious Freedom and Restoration Act ("RFRA") as being in "furtherance of a compelling governmental interest" because the asserted interest in providing "preventive" health services to women is undermined by the significant health dangers of the mandated drugs.

In promulgating the HHS Mandate,[2] the Government selectively ignored and wholly disregarded a large body of relevant, widely available, scientifically sound research showing that the mandated drugs

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[1] Counsel for all parties received timely notice and have consented to the filing of this brief. Their consent letters are on file with the Clerk. No counsel for any party authored any part of this brief, nor contributed monetarily to the brief's preparation or submission.

[2] *Certain Preventive Services Under the Affordable Care Act*, 77 Fed. Reg. 8725 (February 15, 2012) (hereinafter "HHS Mandate").

pose dangerous risks to women's health. The research surveyed for this Court shows that some of the contraceptive drugs have been classified as carcinogens, and that each of the contraceptive drugs and devices have been shown to significantly increase risks of other serious health conditions, including HIV, stroke and heart attack.

SUMMARY OF ARGUMENT

Under the Religious Freedom Restoration Act, the HHS Mandate can survive only if it is "in furtherance of a compelling governmental interest" – which the Government asserts here as its interest in expanding access to "preventive" healthcare to promote women's health.

Amicus demonstrates that the HHS Mandate fails the "furtherance" test of any purported interest in preventive medicine because it *increases* risk of cancer and other serious disease instead of decreasing it.[3]

[3] Medical and science advisors who assisted counsel in the survey of studies presented in this brief include **John M. Thorp, Jr., M.D.**, women's health researcher, professor, and Ob-Gyn director of the UNC-Chapel Hill Women's Primary Healthcare; **Mary Davenport, M.D.**, obstetrician/gynecologist and president of AAPLOG; **Angela Lanfranchi, M.D., F.A.C.S.**, breast surgical oncologist, and co-founder of the Breast Cancer Prevention Institute; and **Maureen L. Condic, Ph.D.**, research scientist at the University of Utah. All universities are listed for purposes of

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This brief is presented to the Court to highlight that the Government, in promulgating the HHS Mandate, relied on a biased and incomplete Institute of Medicine report that selectively disregarded a large body of relevant, widely available, scientifically sound research. *Amicus* presents a partial survey of this robust body of relevant evidence showing that the mandated contraceptives,[4] which are in fact steroids, have biological properties that significantly increase women's risks of breast, cervical, and liver cancer, stroke, and a host of other diseases, including the acquisition and transmission of human immunodeficiency virus ("HIV").

These increased risks have been recognized by reputable national and international medical authorities, including the research arm of the World Health

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identification only; this brief in no way represents the views of the named universities, nor of any of its employees.

[4] The term "contraceptive" as used in this brief reflects terminology used by the Government in the HHS Mandate. *Amicus*, however, acknowledges the religious objection by Petitioners of the capacity of some of the so-called "contraceptive" drugs and devices to terminate the life of a human being at the embryonic stage of development, and thus act as an abortifacient. *See, e.g.*, Miech, R., *Immunopharmacology of ulipristal as an emergency contraceptive*, 3 Intl. Journal of Women's Health 391 (2011) ("When unprotected intercourse and the administration of ulipristal occur at or within 24 hours of ovulation, then ulipristal has an abortifacient action."); *see also*, Rebecca Peck, M.D., and Rev. Juan R. Vélez, M.D., *The Postovulatory Mechanism of Action of Plan B: A Review of the Scientific Literature*, National Catholic Bioethics Quarterly 1-40 (Winter 2013).

Organization which has classified combined oral contraceptives as "Group 1: Carcinogenic to Humans." *See* n. 14, *infra*.

Further, the majority opinion in the D.C. Circuit *Gilardi* case expressly cited *Amicus*' brief, noting that despite FDA-approval (FDA issues discussed *infra*, nn. 18-19), the scientific evidence "may actually undermine the government's cause":

> Equally unconvincing is the government's assertion that the mandate averts 'negative health consequences for both the woman and the developing fetus.' From the outset, we note **the science is debatable and may actually undermine the government's cause**. For the potential mother, as one amicus notes, the World Health Organization classifies certain oral contraceptives as carcinogens, marked by an increased risk for breast, cervical, and liver cancers. Br. of the Breast Cancer Prevention Institute, at 8-9.

Gilardi v. United States Dep't of Health & Human Servs., 733 F.3d 1208, 1221 (D.C. Cir. 2013) (emphasis added).

Yet the Government turned a blind eye to evidence regarding cancer and other serious health risks, relying exclusively on the biased 2011 Institute

of Medicine report that touted only its possible benefits (as discussed in Section A).[5]

Section I sets forth the background of how the Department of Health and Human Services justified including the objectionable drugs in the HHS Mandate as necessary for women's "preventive services." Section A then sets forth the ignored evidence regarding the significant health dangers of oral contraceptive pills, and Section B sets for the ignored evidence regarding health dangers of "long-acting contraceptives," such as injections, implants and IUDs. Section C provides the Court with ignored data showing that the incidence of the cancers that combined oral contraceptives may *cause* far exceed the incidence of cancers that they may *prevent*, as well as presenting the ignored evidence of the alarming increased risks to teenage girls.

Amicus brings this evidence to the Court's attention to demonstrate how the HHS Mandate coerces religious objectors to collaborate in the provision of drugs that not only violate their consciences, but that also increase the risk that women will suffer from cancer and other serious diseases. Consequently, *Amicus* respectfully requests that this Court find that the HHS Mandate does not – and cannot – "further"

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[5] *Gilardi*, *supra*, 733 F.3d at 1221 (The D.C. Circuit's majority opinion stated that "the government has neither acknowledged nor resolved these contradictory claims [of the evidence of increases in risk of breast, cervical and liver cancers with other research touting benefits].").

the Government's asserted compelling interest in promoting the health of women and children. Therefore, the HHS Mandate must fall in light of the free exercise rights of the parties before this Court.

ARGUMENT

I. The HHS Mandate Cannot Meet the Religious Freedom and Restoration Act Requirement of Being in "Furtherance" of the Purported Compelling Interest in Promoting Women's Health Because the Government Selectively Ignored Widely Recognized Research Showing that the Mandate's Contraceptive Drugs and Devices Significantly Increase Risks of Cancer and Other Serious Disease.

The Religious Freedom Restoration Act ("RFRA") prohibits the federal Government from substantially burdening a person's exercise of religion, except when the Government can, among other things "demonstrat[e] that application of the burden to the person (1) is in furtherance of a compelling governmental interest; and (2) is the least restrictive means of furthering that compelling governmental interest." 42 U.S.C. § 2000bb-1(b). This survey demonstrates that the HHS Mandate fails the "furtherance" test of any purported interest in preventive medicine because it increases risk of cancer and other serious disease instead of decreasing it.

On August 1, 2011, pursuant to the Affordable Care Act,[6] the Government agency known as HRSA (Health Resources and Services Administration) adopted in full the guidelines[7] recommended by a report of the non-profit, non-governmental organization known as the Institute of Medicine ("IOM").[8]

After a mere nine pages of one-sided assertions and other methodological flaws,[9] the 2011 IOM

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[6] *The Patient Protection and Affordable Care Act*, Pub. L. No. 111-148, 124 Stat. 119 (2010) requires all group and individual health plans to include coverage for certain preventive services without cost-sharing, including "for women, such additional preventive care and screenings . . . as provided in comprehensive guidelines supported by [the Health Resources and Services Administration ('HRSA')]." 42 U.S.C. § 300gg-13.

[7] Health Resources and Services Administration ("HRSA"), *Women's Preventive Services: Required Health Plan Coverage Guidelines*, *available at* http://www.hrsa.gov/womensguidelines/ (all Internet sites last visited January 22, 2014).

[8] Inst. of Med., *Clinical Preventive Services For Women: Closing the Gaps* (2011) ("2011 IOM Report"), *available at* http://www.nap.edu/catalog.php?record_id=13181 In developing its guidelines, IOM invited a select number of groups to make presentations on the preventive care that should be mandated by all health plans. They included groups that vigorously advocate for abortion, contraceptives and abortifacient drugs including the Guttmacher Institute, the National Women's Law Center, and Planned Parenthood Federation of America. No groups that oppose government-mandated coverage of contraception, sterilization, abortion, and related education and counseling were among the invited presenters. *See id.* at 217-221.

[9] For a comprehensive survey of the disproven ideological assumptions and other methodological flaws of the 2011 IOM Report, *see generally* Helen M. Alvare, *No Compelling Interest: The 'Birth Control' Mandate & Religious Freedom*, 58 VILLANOVA

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Report recommended that "preventive services" for women include all FDA-approved contraceptive methods, sterilization procedures, and patient education and counseling. FDA-approved contraceptive methods include diaphragms, oral contraceptive pills, emergency contraceptives, and intrauterine devices.[10] Notably, the IOM Report completely ignored the highly relevant and widely available scientific research establishing significant *increased* health risks of hormonal contraceptives, as set forth below. Consequently, it did not even attempt to establish that the putative health benefits of hormonal contraceptives outweighed the significantly increased health risks.

In its HRSA publication, the Government expressly and exclusively relied on the biased and unreliable IOM Report as the basis for including contraceptive drugs and devices in its definition of women's "preventive" health services.[11] That publication

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L. REV. 379 (2013); *see also* Karen A. Jordan, *The Contraceptive Mandate: Compelling Interest or Ideology* (December 11, 2013), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2366466; *Dissenting Opinion of Anthony Lo Sasso*, 2011 IOM Report at 231-33 ("The view of this dissent is that the committee process for evaluation of the evidence lacked transparency and was largely subject to the preferences of the committee's composition. . . . This dissent views the evidence evaluation process as a fatal flaw of the Report particularly in light of the importance of the recommendations for public policy and the number of individuals, both men and women, that will be affected."

[10] 2011 IOM Report, at 102-10.

[11] HRSA, *Women's Preventive Services: Required Health Plan Coverage Guidelines*, *supra* n. 7.

indicated the Government's asserted interest in "women's health and well-being" by expanding access to "preventive services that have *strong scientific evidence of their health benefits*."[12]

Yet, the Government's reference to "strong scientific evidence" of health benefits is an empty assertion. In truth, the contraceptive mandate requires coverage of "synthetic, anabolic, carcinogenic, non-biodegradable sex steroid drugs" that endanger women's health, as well as environmental public health.[13]

Surveyed below are citations to a sampling of the robust body of peer-reviewed research studies that the Government and the IOM Report on which it relied completely ignored. This evidence establishes that contraceptive steroids significantly increase a woman's risk of heart attack, blood clots, stroke, breast cancer, cervical cancer, liver tumors, sexually transmitted infections and the contracting and transmission of human immunodeficiency virus ("HIV"), along with a host of other diseases. This evidence is

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[12] *Id.*

[13] In addition to endangering the women who ingest them, contraceptive steroids, which are not biodegradable, also place the environment and society at large at risk once released into waste water after excretion though urine. The effects of this contamination have been increasingly studied in recent years, but they are largely unknown. Joel Brind, Ph.D., *Consuming Secondhand Steroids: The Contraceptive Pollution of Nature*, 34 Ethics & Medics 5 (May 2009).

recognized by national and international health agencies, including the International Agency for Research on Cancer ("IARC") that is part of the World Health Organization. In fact, after a worldwide research review whose results were published 2007, the IARC recognized combined oral contraceptives as "carcinogenic to humans," classified not just as "possible" carcinogens (Group 2B), and not just as "probable" carcinogens (Group 2A), but as carcinogens, period (Group 1: carcinogenic to humans).[14]

The survey below documents significantly increased risks (sometimes double, triple and higher). Even when the initial risk is small, the impact when applied to the tens of millions of women who will be incentivized to ingest these carcinogens based on the "no-cost" requirements of the HHS Mandate will as a matter of logic result in significantly adverse impact on women's health – contrary to the Mandate's purported compelling interest in improving women's "preventive" healthcare.

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[14] In 2007, combined oral contraceptives were classified as "Group 1: Carcinogenic to Humans" for breast, cervical and liver cancers by the World Health Organization's International Agency on Research of Cancer ("IARC"). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Combined Estrogen-Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy* 91:174-84 (2007), http://monographs.iarc.fr/ENG/Monographs/vol91/mono91.pdf (IARC quotation *infra* n. 25); *See also* Kathleen T. Ruddy, M.D., *World Health Organization Warns: Birth Control Pills Cause Breast Cancer* (June 25, 2011), http://breastcancerbydrruddy.com/?p=2808.

In fact, many of the below surveyed studies that were ignored by the Government in implementing the HHS Mandate were previously funded by the Government's own National Institutes of Health, and recognized on the fact sheets of the National Cancer Institute. And most ironically, the Department of Justice in the *Hobby Lobby* case acknowledged in its own brief that hormones used in certain contraceptives are "associated with side effects such as high blood pressure, blood clots, heart attacks, or strokes." *Burwell v. Hobby Lobby Stores, Inc.*, 134 S.Ct. 2751 (2014), Br. of the United States at p. 48 (January 10, 2014) (arguing why the abortifacient non-hormonal copper IUD must be included as a mandated option despite Hobby Lobby's religious objection).

Yet this medical evidence remained wholly unaddressed by the incomplete and poorly sourced 2011 Institute of Medicine ("IOM") report, which was relied upon exclusively by the Government in finalizing the HHS "Preventive Services" Mandate. *See* HRSA, *Women's Preventive Services: Required Health Plan Coverage Guidelines*, *supra* n. 7.

Because of the large body of evidence regarding serious health risks, along with the fact that fertility and pregnancy are not disease states, the mandate of hormonal contraceptives "fail[s] the most important test of preventive medicine: they increase risk of

disease instead of decreasing it."[15] Therefore, the Government simply cannot demonstrate that application of the HHS Mandate to objecting employers "is in furtherance of a compelling governmental interest" as required by RFRA.[16]

While the Government's interest in "preventive services" for "women's health and well-being" may be valid, its act of coercing objecting employers to cover drugs that significantly increase risks to women's health certainly fails to further that interest. As explained by this Court, "We do not doubt the validity of these interests, any more than we doubt the general interest in promoting public health and safety . . . but under RFRA **invocation of such general interests, standing alone, is not enough**." *Gonzales*

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[15] Rebecca Peck, M.D., C.C.D. and Charles W. Norris, M.D., *Significant Risks of Oral Contraceptives* (*"OCPs"*), 79(1) The Linacre Quarterly 41, 42 (February 2012).

[16] In addition to the Government's not having met its burden under RFRA, the failure of the IOM Report to consider or even balance the putative benefits with the increased health risks reveals that the Mandate is "arbitrary and capricious" under the Administrative Procedures Act ("APA"). The judicial standard for review under the APA "arbitrary and capricious" standard provides, "An agency rule would be arbitrary and capricious if the agency . . . **entirely failed to consider an important aspect of the problem**. . . ." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co*., 463 U.S. 29, 43 (1983) (emphasis added). Here, the HHS Mandate is arbitrary and capricious by virtue of the fact that the Government "entirely failed to consider" that the mandated drugs *increase* risk of disease rather than prevent disease.

v. O Centro Espirita Beneficiente Uniao do Vegetal, 546 U.S. 418, 438 (2006) (emphasis added).

It is a violation of religious liberty for religious institutions or religiously observant employers to be coerced by the Government to provide no-cost coverage for drugs that not only violate their rights of conscience, but that also expose women and girls to serious and often life-threatening health risks, all in the name of promoting public health.

A. The IOM Report Selectively Included Only Research Showing Potential Benefits of Oral Contraceptive Pills, and Completely Failed to Even Recognize Research Showing the Pill's Increased Risks of Cancer and Other Serious Disease.

Amicus research organization presents below a survey of the large body of highly relevant peer-reviewed scientific research – completely absent from the IOM Report relied on by the government – that demonstrates the significantly increased health risks associated with the mandated drugs. Rather than address and balance the significantly increased risks of breast, cervical and liver cancers, or even the increased risks of HIV and other life-threatening diseases outlined below, the 2011 IOM Report selectively focused only on the benign "non-contraceptive benefits of hormonal contraception includ[ing] treatment

of menstrual disorders, acne or hirsutism (excessive hairiness on women), and pelvic pain."[17] Where the IOM Report does address cancer risks, it selectively cites studies that show cancers that contraceptives may help prevent, but that occur with much lower incidence and mortality than the cancer risks it increases. *See* Section IC, *infra.*

Amicus recognizes that while non-profit organizations and individuals should not be forced to provide coverage for drugs that they consider immoral, women in our pluralistic society remain free to face the attendant health risks that come with choosing to use hormonal contraceptives. While such drugs have been FDA-approved as effective for the intended use of avoiding pregnancy, it should be noted that more than a dozen drugs have been taken off the market since 1997 due to severe side effects, injuries or deaths.[18] In fact, FDA-misconduct was recently documented in relation to the contraceptive known as "Yaz."[19] Thus, FDA-approval is not the final word on

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[17] 2011 IOM at 107.

[18] PBS Frontline, *Dangerous Prescription* (November 2003), http://www.pbs.org/wgbh/pages/frontline/shows/prescription/.

[19] In 2012, the *Washington Monthly*, which conducted an investigation with the assistance of the *British Medical Journal*, said the FDA neglected in December 2011 to give a report prepared by former FDA commissioner Dr. David Kessler to the advisory committee responsible for reviewing the safety of products containing the hormone drospirenone, which Bayer uses in its oral contraceptives known as Yaz and Yasmin. As an expert witness in a lawsuit filed against Bayer on behalf of plaintiffs claiming to have been injured by those Bayer oral contraceptives, Dr.

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safety, nor was FDA-approval dispositive in the HHS inquiry of whether a drug should be mandated as "preventive" healthcare. Indeed, media reports regularly document FDA scandals and controversies.

The following is a non-exhaustive survey of the completely ignored but highly relevant medical studies documenting the cancer risks and significantly increased health risks of other serious and life-threatening diseases:

1. **Higher risk of heart attack, stroke & cardiovascular complications.** Among women with no conventional risk factors for heart disease, those who take oral contraceptives

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Kessler cited Bayer's internal corporate reports and accused it of concealing data showing blood clot risks among users of those drugs.

According to the *Washington Monthly*, "A series of studies published in *BMJ* have shown that users of pills containing drospirenone have an increased risk of blood clots, which can cause deep vein thrombosis, pulmonary embolism, stroke, heart attack and death. And thousands of women have filed a lawsuit against Bayer, saying they were injured by Yaz or Yasmin. . . . The FDA's decision not to reveal its advisors' relationships with the drugs' manufacturers and Bayer raises serious questions about the agency's treatment of potential conflicts of interest, a historically problematic area for the department." Lenzer J. and Epstein K., *The Yaz Men: Members of FDA panel reviewing the risks of popular Bayer contraceptive had industry ties*, Washington Monthly (January 9, 2012), http://www.washingtonmonthly.com/ten-miles-square/2012/01/the_yaz_men_members_of_fda_pan034651.php#.

have twice the risk of heart attack.[20] Those with hypertension had five times the risk; those who smoked, 12 times the risk; those who had diabetes, 16 times the risk; those who had high cholesterol, 23 times the risk.[21] A meta-analysis of 16 studies found that women who used oral contraceptives had nearly three times the risk of ischemic stroke; for those with risk factors such as high blood pressure or migraine headaches, the risk was significantly higher.[22] Hormonal contraceptives also lead to significantly higher incidence of deep venous thrombosis[23] and pulmonary embolism.[24]

2. **Higher risk of breast cancer.** The World Health Organization's International Agency on Research of Cancer ("IARC") 2007 report concludes that estrogen-progestin combination drugs (the Pill) are a Group 1 carcinogen

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[20] B.C. Tanis, et al., *Oral contraceptives and the risk of myocardial infarction*, 345 New England Journal of Medicine 1787 (2001).

[21] *Id.*

[22] L.A. Gillum, *Ischemic stroke risk with oral contraceptives*, 284 JAMA 72 (2000).

[23] A. van Hylckama Vlieg, et al., *Venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study*, 339 BMJ 2921 (2009).

[24] O. Lindegaard, et al., *Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogens. Danish cohort study 2001-9*, 343 BMJ 6423 (2011).

for breast, cervical, and liver cancers.[25] A 2006 meta-analysis published in the journal *Mayo Clinic Proceedings* showed a 44% increased risk of premenopausal breast cancer in women who took oral contraceptives before first full term pregnancy.[26] A 2009 study showed a 3.2-fold increased risk of triple negative breast cancer, the most difficult and deadly form of breast cancer to treat, in women taking oral contraceptives; and the same study showed an even more alarming 6.4-fold increased risk of that deadly form of breast cancer in teenagers who started

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[25] International Agency for Research on Cancer ("IARC"), 2007 Monograph 91 at 175, *supra* n. 14:

> There is *sufficient evidence* in humans for the carcinogenicity of combined oral estrogen-progestogen contraceptives. This evaluation was made on the basis of increased risks for cancer of the breast among current and recent users only, for cancer of the cervix and for cancer of the liver in populations that are at low risk for hepatitis B viral infection.
>
> There is *evidence suggesting lack of carcinogenicity* in humans for combined oral estrogen-progestogen contraceptives in the endometrium, ovary and colorectum. There is convincing evidence in humans for their protective effect against carcinogenicity in the endometrium and ovary.

It is telling to note that while the underlying research supporting the protective effect was mentioned in the IOM Report, the underlying research supporting the increased risk for cancer of the breast, cervix and liver were never even mentioned.

[26] C. Kahlenborn, et al., *Oral contraceptive use as a risk factor for premenopausal breast cancer: A meta-analysis*, 81 Mayo Clinic Proc. 1290 (2006).

taking oral contraceptives before age 18.[27] And it is important to note that although the risk of uterine and ovarian cancers appears lower for women taking contraceptives, there is four times more breast cancer in women than uterine and ovarian cancers combined.[28]

3. **Higher risk of cervical cancer.** The Government's own National Cancer Institute ("NCI") recognized studies showing a threefold to fourfold increased risk of cervical cancer:

> In a 2002 report by the International Agency for Research on Cancer . . . data from eight studies were combined to assess the association between oral contraceptive use and cervical cancer risk among women infected with the human papillomavirus ("HPV"). Researchers found a nearly threefold increase in risk among women who had used oral contraceptives for 5 to 9 years compared with women who had never used oral contraceptives. Among women who had used oral contraceptives for 10

[27] J. Dolle, et al., *Risk factors for triple negative breast cancer in women under the age of 45*, 18 Cancer Epidemiol. Biomarkers Prev. 1157 (2009).

[28] *See* Cancer Statistics by Cancer Type, Centers for Disease Control, *available at* http://www.cdc.gov/cancer/dcpc/data/types.htm (last visited September 20, 2012).

years or longer, the risk of cervical cancer was four times higher.[29]

4. **Higher risk of liver tumors/cancer.** As stated in the Government's own NCI Factsheet, "Oral contraceptive use is associated with an increase in the risk of benign liver tumors [that] have a high risk of bleeding or rupturing." Moreover, "[s]ome studies have found that women who take oral contraceptives for more than 5 years have an increased risk of [malignant liver tumors known as] hepatocellular carcinoma, but others have not."[30]

5. **Greater susceptibility to sexually transmitted infections.** Women taking oral contraceptives are twice as likely to be infected with the genital human papillomavirus ("HPV") virus, leading to cervical cancer, as women not taking oral contraceptives.[31] While the studies on HIV risk and *oral* contraceptives show mixed results, one well-known study finds that women taking the pill are 60% more likely to be infected with

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[29] National Cancer Institute: Oral Contraceptives and Cancer Risk (March 21, 2012) *citing* V. Moreno, et al., *Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study*, 359 Lancet 1085 (2002).

[30] *Id.*, *citing* C. La Vecchia and A. Tavani, *Female hormones and benign liver tumours*, 38 Digestive and Liver Disease 535 (2006).

[31] S. Franceschi, et al., *Genital warts and cervical neoplasia: an epidemiological study*, 48 Br. J. Cancer 621 (1983).

the HIV virus than those who are not.[32] In addition to physiological changes caused by hormonal contraceptives leading to increased susceptibility to sexually transmitted infections ("STIs"), recent studies indicate that increased access to emergency contraceptives leads to behavioral changes, i.e., increased risk-taking in sexual behavior, that not only cancels out any decrease in the rate of unplanned pregnancy among adolescents, but also drives up the rate of STIs.[33]

B. Serious Health Risks of Long-Acting Contraceptives.

As shown by studies and easily predicted by standard microeconomic theory, the "no-cost" element of the HHS Mandate will not only increase use of low-cost pills and emergency contraceptives, it will also increase incentives for women and adolescents to choose the previously cost-prohibitive "long-acting methods," such as injectable contraceptives, implants, and intrauterine devices ("IUDs").[34]

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[32] C.C. Wang, et al., *Risk of HIV infection in oral contraceptive pill users: a meta-analysis*, 21 JAIDS 51 (1999).

[33] *See* S. Girma, et al., *The impact of emergency birth control on teen pregnancy and STIs*, 30 Journal of Health Economics 373 (2011).

[34] *Id.* ("[A]s might be predicted by standard microeconomic theory, increased access to EBC [emergency birth control] induces at least some adolescents to increase their level of risk-taking sexual behaviour and that the reduction in pregnancies

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According to *A Pocket Guide to Managing Contraception* ("*MC*"),[35] methods of long-acting contraception include the following drugs and devices that pose the following increased risks:

(1) **ParaGard© Intrauterine Copper IUD:** The copper IUD can result in **uterine perforation** and other malpositioning that can result in **increased bleeding or pain**, and **injury or damage to the surrounding organs**.[36]

(2) **Mirena© levonorgestrel-releasing IUD:** Unlike ParaGard©, which contains no steroidal hormones, the Mirena© IUD releases levonorgestrel ("LNG") into the uterine environment. In addition to risks of **uterine perforation**, which were the subject of a warning letter sent by FDA to the manufacturer Bayer, Mirena has been linked to **ovarian cysts**, a higher profile for **pelvic**

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from greater use of EBC is being countered by additional pregnancies resulting from this behaviour change.")

[35] N. Zieman, R.A. Hatcher, et al., *A Pocket Guide to Managing Contraception*, Tiger, GA: Bridging the Gap Foundation, 2010, at 37. "*Managing Contraception*" or *MC* is a condensed version of the primary medical textbook on contraception – R.A. Hatcher, et al., *Contraceptive Technology* (20th rev. ed.). Atlanta, GA: Ardent Media, Inc., 2011.

[36] K.P. Braaten, et al., *Malpositioned IUDs: When you should intervene* (*and when you should not*), 24(8) OBG Management 39 (2012), citing B.R. Bernacerraf, et al. *Three-dimensional ultrasound detection of abnormally located intrauterine contraceptive devices which are a source of pelvic pain and abnormal bleeding*, 34(1) Ultrasound Obstet. Gynecol. 110 (2009).

inflammatory disease ("PID"), and irregular bleeding. Also, in the rare case in which a woman conceives while using the Mirena, a resultant loss of pregnancy and a **possible permanent loss of fertility** may result.[37]

Surprisingly, the Government's attorneys in its *Hobby Lobby* brief filed in this Court belatedly admitted that the hormone-releasing IUDs are indeed "associated with side effects such as high blood pressure, blood clots, heart attacks, or strokes." *Burwell v. Hobby Lobby Stores, Inc.*, 134 S.Ct. 2751 (2014), Br. of the United States at p. 48 (January 10, 2014). The Government's counsel made this statement in its brief to this Court to defend why it must include all abortifacient drugs and devices over the religious objections of Hobby Lobby. Yet, such health risks were never acknowledged or balanced in the 2011 IOM Report that claimed that all FDA-approved contraceptives were "safe." 2011 IOM Report at 104-05.

(3) **Implanon©:** This device is a plastic implant rod containing progestogen etonogestrel which is surgically inserted under the skin of the upper arm; it replaced Norplant© which is no longer marketed in the U.S., after over 50,000 women filed lawsuits – including 70

[37] Mirena® Label, Warnings and Precautions; *see also* Uterine Perforation Risk from Mirena, *available at* http://www.womens-health.co.uk/uterine-perforation-risk-from-mirena.html.

class actions – over severity of side effects.[38] In addition to **ectopic pregnancy** risks, the manufacturer warning reports "serious thromboembolic events, including cases of **pulmonary emboli (some fatal)** and **strokes**, in patients using IMPLANON."[39]

(4) **Depo-Provera©:** This is an injectable progestogen intended to last up to three months. A 2012 study reveals that there are now five studies "conducted over a diverse group of countries" that report an increased risk of breast cancer whose upper range is **more than doubled** in women who used Depo-Provera for more than 12 months.[40] Moreover, in addition to this injection's **black box warning on loss of bone mineral density**, Depo-Provera use has been shown to result in a **doubled risk of acquiring and transmitting HIV**, as discussed below.

Disturbingly, the Mandate's "no-cost" coverage will increase use of Depo-Provera, which carries startling increased risks regarding the deadly HIV

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[38] CT, *supra* n. 35.

[39] Implanon© Warnings, *available at* http://www.implanon-usa.com/en/HCP/learn-about-it/get-the-facts/warnings/index.asp.

[40] C. Li, et al., *Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 Years of Age*, 72(8) Cancer Res. 2028 at n. 4-7 (2012) ("with the addition of the results reported here, there are now 5 studies conducted over a diverse group of countries that have observed that recent DMPA use is associated with a 1.5- to 2.3-fold increased risk of breast cancer.").

infection. In October 2011, the *New York Times* gave front-page coverage to the rigorous Heffron study, which was funded by the National Institutes of Health and the Bill & Melinda Gates Foundation.[41] That study had been published in a prestigious peer-reviewed medical journal after the study's presentation had raised alarm among public health advocates months earlier at an international AIDS conference. The Heffron study presented convincing findings that injectable contraceptives have "biological properties" that appear to "**double** the risk that women will become infected with H.I.V.," and further finding that "when it is used by H.I.V.-positive women, their male partners are **twice as likely to become infected** than if the women had used no contraception."[42]

The study focused on Depo-Provera, a drug covered by the HHS Mandate. Of particular note is a statement by the director of the women and foreign policy program at the Council on Foreign Relations: "*If it is now proven that* [*injectable*] *contraceptives are helping spread the AIDS epidemic, we have a major health crisis on our hands.*"[43] There has been no study to dispute the Heffron study, yet this dangerous drug

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[41] R. Heffron, et al., *Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study*, 12 Lancet Infect Dis. 19 (2012) (published online October 2011).

[42] Pam Belluck, *Contraceptive Used in Africa May Double Risk of H.I.V.*, N.Y. Times, October 3, 2011 (covering Heffron study, *supra*, n. 41) (emphasis added).

[43] *Id.* (emphasis added).

is now mandated in health plans as women's "preventive services."

C. The IOM Report Ignores the Fact that the Incidence of the Cancers that Combined Oral Contraceptives May Cause Far Exceed the Incidence of the Cancers that they May Prevent, and also Ignores the Increased Risk to Teenage Girls.

The 2011 IOM Report fails to even recognize the existence of the large body of highly relevant, widely available, scientifically sound, scholarly research surveyed above evidencing a host of adverse health consequences and increased cancer risks resulting from the use of contraceptive drugs and devices. The only consequences acknowledged by the 2011 IOM Report are unnamed "side effects" (which it says are "generally considered minimal"[44]) and low death rates that can be directly linked to contraceptive use.[45] It

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[44] 2011 IOM cites ACOG informational brochures for its benign judgment on the "side effects" of hormonal contraceptives (2011 IOM at 105, 135), neglecting to mention that these brochures additionally contain discussions of the "risks" of oral contraceptives, including, as outlined above, heart attacks, strokes, blood clots, and liver tumors.

[45] 2011 IOM at 105-06; As certainly known by the members of the Institute of Medicine, "causation" of death is notoriously difficult to establish, yet the IOM Report selectively fails to document the peer-reviewed research establishing statistically significant increased risks of deadly diseases.

completely ignores the range of health risks between those extremes, even though the Government itself acknowledges these risks on the National Cancer Institute websites, and indeed funds many of the serious health risk studies discussed above through the National Institutes of Health.[46]

In an amazing display of ideological bias, the only mention by the 2011 IOM Report regarding cancer risks are those that oral contraceptives may prevent – namely endometrial and ovarian cancer.[47] In other HHS Mandate challenges, the Government's *amicus* have pointed to a possible reduction in the risk of colon cancer. But as explained below, even if the disputed preventive effect of oral contraceptives on colon cancer risk is included, the incidence of the cancers that combined oral contraceptives may cause (breast, liver and cervix) far exceed the incidence of the cancers that oral contraceptives may prevent (colon, endometrium and ovaries) in the United States.

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[46] *See, e.g.*, Heffron, *supra*, n. 41, which states: "Funding: US National Institutes of Health and the Bill & Melinda Gates Foundation."

[47] 2011 IOM at 107.

1. The IOM Report Selectively Ignored Studies Showing Increased Incidence of Deadly Cancers

The IOM Report relied on by the Government selectively ignored research showing increased risks of breast, cervical and liver cancer, and reported only on decreased risks of ovarian cancer. This biased report thus ignores the data showing that for the year 2013, the expected incidence of cancers of the breast, liver and cervix among American females will surpass the incidence of cancers of the colon, endometrium and ovarian by 193,050 cases.

The total number of invasive and *in situ* breast cancers are expected to reach 296,980 cases.[48] Cancers of the liver and cervix will reach 20,260 total cases. Together, the incidence of these cancers that are negatively impacted by the carcinogen of combined oral contraceptives will total 317,240 cases.

By contrast, the cancers that oral contraceptives may prevent (endometrial and ovarian) are expected to total 71,800. If the disputed protective effect of oral contraceptives on colon cancer risk is included, then

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[48] The expected number of invasive breast cancers for American females is 232,340. The expected number of *in situ* (early) breast cancers is 64,640. American Cancer Society, *Cancer Facts and Figures 2013*, *available at* http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf (*In situ* breast cancers are reported in small print at the bottom of page 4 entitled, "Estimated number of new cancer cases and deaths by sex, US, 2013").

the total number of expected cancers that oral contraceptives may reduce would climb to 124,190 cases.[49]

The Government's *amicus* in this case may follow the pattern in previous HHS Mandate cases by favorably quoting a 2005 report from the UN/UNFPA/WHO/World Bank.[50] They fail to note that this study

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[49] *Id.* at 4.

[50] UNDP/UNFPA/WHO/World Bank Special Programme of Research, Dev. & Research Training in Human Reprod. ("HRP"), *Carcinogenicity of Combined Hormonal Contraceptives and Combined Menopausal Treatment* 1 (2005) ("Several WHO committees work on creating evidence-based family planning guidelines and on keeping them up-to-date on a continuous basis. They regularly review the safety of COCs (combined oral contraceptives) and assess the balance of risks and benefits of COC use and they have determined that for most healthy women, the health benefits clearly exceed the health risks.").

This statement ignores an important warning issued by the International Agency for Research on Cancer Working Group when it published the following in a 2005 issue of the journal, *Lancet Oncology*:

> Because use of combined contraceptives heightens the risk of some cancers and reduces that of others, it is possible that the overall net public-health outcome could be beneficial, **but a rigorous analysis is needed to show this**. Such an analysis is outside the scope of an IARC monograph meeting and would include quantitative estimates of the age-specific absolute risk at each cancer site, the availability and effectiveness of cancer screening, the availability, effectiveness, and side-effects of cancer treatments, and other health and societal effects, both beneficial and adverse. **Since these factors vary throughout the world, the risk-benefit analysis should be specific to each country and population.**

(Continued on following page)

pre-dates the 2006 *Mayo Clinic Proceedings* meta-analysis,[51] discussed below, as well as two other significant studies from 2009 and 2010 that strongly link use of oral contraceptives with the aggressive, deadly triple-negative breast cancer.

The 2009 study by Dolle, et al. on women under age 45 reports that the risk of triple-negative breast cancer conferred by longer oral contraceptive duration (more than one year) and by more recent use was a statistically significant 4.2-fold increased risk. The authors wrote, "Triple-negative breast cancer constitutes a clinically challenging type of breast cancer that occurs more frequently in younger women (under age 50) and African-American women and is associated with significant aggressiveness as compared with other subtypes."[52]

The 2010 study by Ma, et al. reported a 2.9-fold increased risk for triple negative tumors among *older*

V. Cogliano, Y. Grosse, R. Baan, K. Straif, B. Secretan, F. El Ghissassi, *Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment*, 6 Lancet Oncology 552-553 (2005) (emphasis added).

[51] C. Kahlenborn, F. Modugno, D.M. Potter, W.B. Severs, *Oral contraceptive use as a risk factor for premenopausal breast cancer: A Meta-Analysis*, 81(10) Mayo Clinic Proceedings 1290-1302 (2006), *available at* http://www.ncbi.nlm.nih.gov/pubmed/17036554.

[52] J. Dolle, et al., *Risk factors for triple-negative breast cancer in women under the age of 45 years*, 18(4) Cancer Epidemiol. Biomarkers Prev. 1157-1166 (2009).

women (ages 45-64 years) who started using oral contraceptives before age 18.[53]

2. The IOM Report Ignored the Increased Risks to Teenagers

As discussed more fully below, the worst time in a woman's life to be exposed to a carcinogen is during the "susceptibility window" of the teenager and young adult years. Yet, the HHS Mandate creates incentives for the use of carcinogenic contraceptives by the teenage children of covered employees because the Government mandates that such drugs be provided "without cost-sharing" for enrollees and dependents who are "women of reproductive capacity."[54] The Mandate thus endangers the physical health of the teenaged daughters of covered employees.[55]

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[53] H. Ma, et al., *Use of four biomarkers to evaluate the risk of breast cancer subtypes in the Women's Contraceptive and Reproductive Experiences Study*, 70(2) Cancer Research 575-587 (2010), *available* at http://cancerres.aacrjournals.org/content/70/2/575.long.

[54] 77 Fed. Reg. 8725.

[55] Because sterilization, contraception and abortifacient drugs must be provided without cost-sharing to enrollees and their female dependents who have "reproductive capacity," the HHS Mandate provides no-charge access to employee's minor daughters who have reached the stage of menstruation. Studies show that no-charge access to even emergency contraceptives increases risky and uncommitted sexual behavior. *See generally* S. Girma, et al., *supra*, n. 33.

Not only did the 2011 IOM Report fail to cite or balance the alarming results of the 2009 Dolle study showing a 4.2-fold increased risk of triple negative breast cancer, but it also failed to reveal that the same 2009 study showed an even more alarming 6.4-fold increased risk of the deadly triple-negative breast cancer in teenagers who started taking oral contraceptives before age eighteen.[56]

The IOM Report also fails to account for the fact that teenagers are the least likely group to be aware of the health risks associated with use of hormonal steroids such as oral contraceptives and Depo-Provera, and the least likely to know the medical history of extended family members. The most cancer-susceptible time in a woman's life takes place between the onset of menstruation and first full term pregnancy (known as the "susceptibility window").[57] That is the period when the breasts are growing and nearly all of the breast lobules consist of immature, cancer-susceptible Type 1 and 2 lobules where 95% of all cancers are known to start.

However, by the end of a first full term pregnancy, 85% of the breast lobules are fully mature and permanently cancer-resistant. Genetic changes that take place in the breast lobules during a full term

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[56] J. Dolle, et al., *supra* n. 52, at 1162.

[57] J. Russo and H. Russo, "Development of the Human Mammary Gland," in *The Mammary Gland*, eds. M. Neville and C. Daniel (New York: Plenum Publishing Corporation, 1987).

pregnancy provide lifelong protection against breast cancer.[58] [59] [60] [61] [62]

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[58] J. Russo, G. A. Balogh, I. H. Russo, and the Fox Chase Cancer Center Hospital Network Participants, *Full-Term Pregnancy Induces a Specific Genomic Signature in the Human Breast*, 17(1) Cancer Epidemiology, Biomarkers and Prevention 51-66 (January 2008).

[59] I. Verlinden, N. Güngör, K. Wouters, J. Janssens, J. Raus, and L. Michiels, *Parity-Induced Changes in Global Gene Expression in the Human Mammary Gland*, 14 European Journal of Cancer Prevention 129-137 (2005).

[60] Medical texts and medical authorities agree that delayed first full term pregnancy is a risk factor for breast cancer. Every one-year delay of a first full term pregnancy increases the risk of premenopausal breast cancer by 5% and postmenopausal breast cancer by 3%. *See, e.g.*, Françoise Clavel-Chapelon and Mariette Gerber, *Reproductive Factors and Breast Cancer Risk*, 72(2) Breast Cancer Research and Treatment 107-115 (2002).

[61] In a landmark study, Harvard and other international scientists reported that women who had a first full-term pregnancy at age 35 in comparison with those who had a first full-term pregnancy at age 17 had a three-fold greater risk of breast cancer. MacMahon, B., Cole P., Lin T.M., Lowe C.R., Mirra A.P., Ravnihar B., Salber E.J., Valaoras V.G., Yuasa S., *Age at First Birth and Breast Cancer Risk*, 43 Bull. World Health Org. 209-221 (1970).

[62] "Indeed, if women had larger family sizes and longer lifetime durations of breastfeeding that were typical of developing countries until recently, the cumulative incidence of breast cancer in developed countries is estimated to be reduced by more than half (from 6.3 to 2.7 per 100 women) by age 70 years." V. Beral, et al., *Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease*, 360 Lancet 187-195 (2002).

Indeed, a 2006 meta-analysis of studies on oral contraceptives and breast cancer risk published in the journal *Mayo Clinic Proceedings* reported that "[t]he association between [oral contraceptive] use and breast cancer risk was greatest for parous women who used OCs [oral contraceptives] 4 or more years before FFTP [first full term pregnancy]."[63] The authors reported a statistically significant 52% risk elevation for this group.

The authors also found a statistically significant 44% increased risk of pre-menopausal breast cancer among women who started using oral contraceptives before first full term pregnancy. They explained the biological rationale as follows:

> The results of prior studies and of ours are consistent with the hypothesis that OCs (oral contraceptives) can be carcinogenic, especially when used before FFTP (first full term pregnancy). The nulliparous (nonchildbearing) breast is composed of undifferentiated structures, and it is only during a full-term pregnancy that the breast attains its maximum development. This development occurs in 2 distinct phases, an early growth phase and a late phase of lobular differentiation. The undifferentiated breast structures found in the nulliparous breast may be more susceptible to carcinogens than

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[63] C. Kahlenborn, et al. *Oral contraceptive use as a risk factor for premenopausal breast cancer: A meta-analysis*, 81(10) Mayo Clinic Proceedings, *supra* n. 26, n. 51.

> the more differentiated structures found in the fully developed breast. For example, in Hiroshima and Nagasaki, Japan, nulliparous women who were exposed to radiation from the atomic bomb developed breast cancer far more frequently than women who had already borne children at the time of exposure.[64]

CONCLUSION

In sum, the Government cannot meet the RFRA requirement that the coercive HHS Mandate be in "furtherance" of its asserted compelling interest in promoting women's preventive healthcare. It has completely ignored the mandated drugs' many serious health risks, as well as the established ties between hormonal contraceptives and the cancer epidemic among young healthy women to whom carcinogenic drugs are given for reasons as benign as acne prevention, or, more frequently, to suppress fertility – which is not a disease state.

For the foregoing reasons, *Amicus* Breast Cancer Prevention Institute requests that this Court reverse

[64] *Id.* at 1297.

the decisions of the courts below, and grant Petitioners an exemption from complying with the HHS Mandate.

Respectfully submitted,

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