Clinical Policy Title: Cryopreservation of sperm and embryos

Clinical Policy Number: 12.03.05

Effective Date: October 1, 2015
Initial Review Date: June 17, 2015
Most Recent Review Date: July 20, 2016
Next Review Date: July 2017

Policy contains:
- Cryopreservation.
- Gonad.
- Gonadotoxin.
- Onco-infertility.

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas District of Columbia has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas District of Columbia’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas District of Columbia when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas District of Columbia’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas District of Columbia’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas District of Columbia will update its clinical policies as necessary. AmeriHealth Caritas District of Columbia’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas District of Columbia considers once-per-lifetime cryopreservation of sperm and embryos in preserving fertility in post-pubertal men or women facing infertility due to chemotherapy or other gonadotoxic therapies to be clinically proven and, therefore, medically necessary.

Limitations:

AmeriHealth Caritas District of Columbia considers cryopreservation of sperm and embryos for purposes of circumventing the reproductive aging process to be investigational and, therefore, not medically necessary.

All other uses of cryopreservation of sperm and embryos are considered to be investigational and, therefore, not medically necessary.

Infertility services are always subject to legislative mandate. Some states mandate benefit coverage for certain infertility services, including cryopreservation. Where legislative mandates exist, they supersede benefit plan design.
Alternative covered services:

- Reproductive endocrinology to maximize the reproductive potential of cancer patients and survivors.
- Ovarian transposition to physically move the ovaries out of the pelvis through surgical techniques in cases where pelvic radiation is required, to minimize the damaging effects of ionizing radiation on the ovaries.
- Gonadotropin agonist injections to chemically regulate the ovaries or testes.

**Background**

Therapies to treat medical conditions such as cancer may compromise fertility. Chemotherapy agents linked to fertility issues include:

- Cisplatin.
- Cyclophosphamide.
- Chlorambucil.
- Busulfan.
- Procarbazine.
- Carmustine.
- Lomustine.
- Mechlorethamine.
- Melphalan.

Radiation therapy may have potential side effects that affect fertility issues:

- In females, reproductive organs may suffer damage by direct irradiation or scattered radiation even after shielding.
- In males, the spermatogonia are extremely sensitive to radiation regardless of age.

Radical surgical procedures for cancer may have adverse effects upon reproductive capacity and fertility:

- Oncologic surgery for uterine, ovarian, bladder or colon cancer in females.
- Oncologic surgery for prostate, bladder or colon cancer in men.

Long-term treatment of estrogen-receptor positive breast cancer also has side effects that influence fertility decisions.

Options to preserve fertility include cryopreservation of sperm and embryos. Cryopreservation is the process of cooling and storing cells, tissues or organs at very low or freezing temperatures to save them for future use. It is used to preserve sperm, semen, oocytes (eggs), embryos, ovarian tissue or testicular tissue as an option for post-pubertal men and women who wish to or must delay reproduction for various reasons, including the need to undergo therapies that threaten their reproductive health, such as cancer treatment.
Currently, there are no fertility preservation options available for the pre-pubertal male or female.

**Searches**

AmeriHealth Caritas District of Columbia searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

Searches were conducted on June 16, 2016, using the terms "embryo," "egg," "preservation," "freezing," "banking," "oocyte," "sperm" and "cryopreservation."

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

A contemporary narrative review (Rodriguez-Wahlberg 2014) addressed specifically and in depth the threat to fertility from cancer treatment and concluded, "In adult patients, cryopreservation techniques, such as sperm banking for males and embryo and oocyte banking for females, both of which are now established methods, may also be considered prior to (treatment)."

The National Comprehensive Cancer Network Clinical Practice Guidelines for Adolescent and Young Adult Oncology (NCCN 2014) include oophoropexy for females receiving radiation therapy. For individuals where treatment can be delayed long enough for a cycle of oocyte stimulation, then embryo cryopreservation should be discussed.

The Practice Committees of the American Society for Reproductive Medicine (ASRM 2013) published a committee opinion on fertility preservation for individuals undergoing gonadotoxic therapy or gonadectomy, which includes embryo cryopreservation as an "established modality for fertility preservation."
The American Society of Clinical Oncology (Loren 2013) conducted a systematic review of the evidence on fertility preservation for adults and children with cancer. Sperm, embryo and oocyte cryopreservation are considered standard practice.

The American Cancer Society (ACS 2013) considers sperm banking an effective way for men who have gone through puberty to store sperm for future use. In general, sperm collected before cancer treatment is just as likely to start a pregnancy as sperm from men without cancer. Sperm banking has resulted in thousands of pregnancies, without unusual rates of birth defects or health problems in the children. Once sperm is stored, it remains good for many years.

The National Institute for Health and Care Excellence (NICE 2013) addresses cryopreservation issues in adults and adolescents:

- When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos or oocytes.
- Offer sperm cryopreservation to men and adolescent boys who are preparing for medical cancer treatment likely to make them infertile.
- Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) preparing for medical cancer treatment likely to make them infertile if:
  - They are well enough to undergo ovarian stimulation and egg collection.
  - This will not worsen their condition.
  - Enough time is available before the start of their cancer treatment.

A narrative review (Dillon 2012) concluded that, with improved survival rates for childhood cancers, long-term implications with regard to fertility were gaining importance. However, there are at present no fertility preservation measures available to pre-pubertal boys and only experimental ovarian tissue cryopreservation available to pre-pubertal girls.

Laws governing disputes about cryopreserved embryos vary by state. Some states (e.g., Tennessee) take a balance-of-interests approach. A 1992 decision argued that, in the absence of a prior agreement about the disposition of pre-embryos, the party wishing to avoid procreation should prevail if the other party had a reasonable alternative option for becoming a parent. The court ordered that the pre-embryos of a divorcing couple should be discarded, finding in favor of the former husband, who did not wish to become a father.

In the wake of this precedent-setting case, many states, such as New York and Texas, began to opt for contractual enforcement. In a 1998 dispute between a divorcing couple, the Court of Appeals in Albany, NY, followed the contract that the couple had signed with the clinic.

In another approach, Iowa requires mutual consent before embryos can be disposed of or used.
Massachusetts will not enforce contracts in such cases. After a 2000 divorce dispute, the Massachusetts Supreme Court ruled, “As a matter of public policy, we conclude that forced procreation is not an area amenable to judicial enforcement.”

In the most recent court decision in the Szafranski-Dunston case in May 2014, Judge Sophia Hall argued that the decision should be based on a contract; but, if there is no contract, a balance of interests should be used. Hall argued that a phone conversation between Dunston and Szafranski was an oral contract. She further noted that the case was likely to be appealed, and that, were it to be considered on a balance of interests, Dunston’s (the mother) should prevail because she could not have a genetically related child by any other means: “The Court … finds that Karla’s desire to have a biological child in the face of the impossibility of having one without using the embryos, outweighs Jacob’s privacy concerns,” Hall wrote.

Costs for maintaining cryopreserved samples of sperm or embryo are modest. Query produced four examples for comparison purposes:

1. At Fairfax, VA, Cryobank (a national chain with locations in Austin, Houston, Philadelphia and Roseville, MN) the following fee schedule for storage and release of semen specimens prevails:*  
   - Fees are by account regardless of the number of vials stored.  
   - Semen specimens/patient — monthly: $40.  
   - Semen specimens/patient — Prepaid one year: $395.  
   - Semen specimens/patient — Prepaid two years: $670.  
   - Semen specimens/patient — Prepaid three years: $985.  
   - Semen specimens/patient — Prepaid five years: $1,340.  
   - Semen specimens/patient — Prepaid 10 years: $2,400.  
   - Semen specimen release (handling): $45.

2. At ReproTech Ltd. (RTL) a national chain with locations in Texas, Minnesota, Florida and Nevada) the following fee schedule prevails:* 

<table>
<thead>
<tr>
<th>Sperm, oocytes (eggs) or ovarian tissue:</th>
<th>Standard fee</th>
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</thead>
<tbody>
<tr>
<td>Billing period</td>
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<tr>
<td>Quarterly</td>
<td>$75</td>
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<tr>
<td>One year</td>
<td>$275</td>
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<td>Two years</td>
<td>$490</td>
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<td>Three years</td>
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<tr>
<td>Five years</td>
<td>$1,050</td>
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<tr>
<td>10 years</td>
<td>$1,905</td>
</tr>
</tbody>
</table>

| Embryos:                                     | Standard fee |
| Billing period                               |              |
|                                             |              |


<table>
<thead>
<tr>
<th>Billing period</th>
<th>Standard fee</th>
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<tbody>
<tr>
<td>Quarterly</td>
<td>$106</td>
</tr>
<tr>
<td>One year</td>
<td>$400</td>
</tr>
<tr>
<td>Two years</td>
<td>$700</td>
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<td>Three years</td>
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<tr>
<td>Five years</td>
<td>$1400</td>
</tr>
<tr>
<td>10 years</td>
<td>$2645</td>
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</table>

There is a surcharge for "potentially infectious" specimen handling at RTL.

*Neither company bills for its services directly by mail or electronic means to insurers. Both offer the client a receipt that can be submitted to the client's insurer for reimbursement.

3. Specialists in Reproductive Medicine & Surgery, P.A. of Ft Myers, FL, maintain this fee schedule (subject to change without notice):

   Cryopreservation, transportation and storage fees:

   Probable oocyte cryopreservation fees: $1,400.00

   **Oocyte storage fee — first year (paid directly to storage facility): $275.00

   Federal Express: $215.00

   Subtotal: $1,890.00

   ** These fees are paid directly to the long-term storage facility. Credit card information will be obtained on or before baseline.

The company will request pre-authorization from the member for infertility services. Failing authorization, the company accepts payment at point of care with a credit card which is kept on file for future billing of services.

4. Alcor Life Extension Foundation (ALCOR), which identifies itself as the "world leader in cryonics, cryonics research and cryonics technology," is located in Scottsdale, AZ. Membership includes life insurance for candidates in good health and eligibility, which will pay for cryopreservation of the whole body.

A growing number of cryopreservation advocacy groups have sprung up to assist individuals with concerns, and a list of worldwide resources is appended (Appendix A).
Members with concerns regarding cryopreservation maintenance after insurance benefit is terminated or exhausted may be offered these support groups as a resource for their needs.

AmeriHealth Caritas District of Columbia members may also find the clinical trials ongoing in regards to onco-infertility to be of benefit.

**Policy updates:**

A retrospective study (Slabbert 2015) compared cryoprotectant-free vitrification to conventional cryopreservation protocols. Cryoprotectant-free vitrification is a simple and cost-effective method for the storage of human spermatozoa without the use of conventional cryoprotectants, by plunging the sperm suspension directly into liquid nitrogen. As a result, solidification of living cells without the formation of ice crystals is achieved during cooling. Semen samples (n = 35) were processed using a discontinuous density-gradient centrifugation method, and washed samples were split into two aliquots and cryopreserved either by means of cryoprotectant-free vitrification (sucrose + 1% albumin) or conventional slow freezing (TEST-yolk buffer). TEST-yolk buffer is a semen extender and cryobuffer that can be paired with glycerol to achieve high sperm motility and viability. No significant differences were observed in the sperm motility parameters (p > 0.05). Lower percentages of DNA fragmentation (2.79% ± 1.017% versus 3.86% ± 1.38%; p < 0.01) were also observed when comparing cryoprotectant-free vitrification to conventional cryopreservation. The authors concluded that cryoprotectant-free vitrification was promising as a rapid alternative to conventional methods of gamete cryopreservation.

In a narrative review, Keskintepe (2015) considered long-term preservation of mammalian sperm at suprazero temperatures by the freeze-drying of sperm samples. Although freeze-drying results in immotile and membrane-compromised sperm, intracytoplasmic sperm injection (ICSI) can be used to introduce such an immotile sperm into an oocyte and thus start the fertilization process. The authors noted that improved freeze-drying protocols preserve chromosomal integrity and oocyte-activating factor(s) at 4 °C for several years and at ambient temperature for approximately 1 month, which permits shipping freeze-dried samples at ambient temperature. The authors presented a protocol for simple freeze-drying of mammalian sperm in order to facilitate adoption of their methods.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Method, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slabbert (2015)</td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Study compared cryoprotectant-free vitrification to conventional cryopreservation protocols.</td>
</tr>
<tr>
<td></td>
<td>• Semen samples (n = 35) were processed using a discontinuous density-gradient centrifugation method.</td>
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<td></td>
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</tbody>
</table>
| Keskintepe (2015) | • No significant differences were observed in the sperm motility parameters ($p > 0.05$).  
• Cryoprotectant-free vitrification was advocated as a rapid and promising alternative to conventional methods. |
| Rodriguez-Wahlberg (2014) | **Key points:**  
• Narrative review of long-term preservation of mammalian sperm at suprazero temperatures.  
• Authors concluded that ICSI can be used to introduce such an immotile sperm into an oocyte and thus start fertilization.  
• Freeze-drying protocols preserve chromosomal integrity and oocyte-activating factor(s) at 4°C for several years and at ambient temperature for approximately 1 month. |
| NCCN (2014) | **Key points:**  
• Advocates ovarian transpositioning for females receiving radiotherapy and discussion of cryopreservation of embryo for fertility preservation. |
| ASRM (2013) | **Key points:**  
• Advice on fertility preservation for individuals undergoing gonadotoxic therapy or gonadectomy.  
• Identifies embryo cryopreservation as an "established modality for fertility preservation." |
| Loren (2013) | **Key points:**  
• Sperm, embryo and oocyte cryopreservation are considered standard practice. |
| ACS (2013) | **Key points:**  
• Cites sperm banking an effective way for men who have gone through puberty to store sperm for future use. |
| NICE (2013) | **Key points:** |
Fertility problems: assessment and treatment

- Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile.
- Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if:
  - They are well enough to undergo ovarian stimulation and egg collection.
  - This will not worsen their condition.
  - Enough time is available before the start of their cancer treatment.

Dillon (2012)

Pediatric and young adult patients and oncofertility

Key points:

- Improved survival rates for childhood cancers with regard to fertility are gaining importance.
- At present no fertility preservation measures are available to pre-pubertal boys and only experimental ovarian tissue cryopreservation available to pre-pubertal girls.

Glossary

Cryopreservation — A process in which sperm and embryos are frozen in liquid nitrogen and may be thawed for future use.

Gonad — A reproductive cell-producing gland, such as an ovary.

Gonadotoxic — Having a deleterious effect on the gonads, such as chemotherapy or radiation therapy.

Onco-infertility — The growing field of cancer-related infertility.

References

Professional society guidelines/others:

ALCOR Life Extension Foundation. Landing page. Website: http://www.alcor.org/


**Peer-reviewed references:**

Dillon K., Gracia R. Pediatric and young adult patients and oncofertility. *Current Treatment Options in Oncology.* 13 (2) (pp 161 – 173), 2012.


**Clinical trials:**

Searched clinicaltrials.gov on 16 June 2016 using terms “cryopreservation,” “embryo,” and “sperm” | Open Studies. Six studies found, none were relevant.
CMS National Coverage Determinations (NCDs):

No NCDs for cryopreservation to preserve fertility in adult cancer survivors were identified on the CMS website. However, Medicare does cover reasonable and necessary services associated with treatment for infertility:


Local Coverage Determinations (LCDs):

No LCDs were identified at this time.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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<tr>
<th>CPT Code</th>
<th>Description</th>
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</tr>
<tr>
<td>89259</td>
<td>Cryopreservation; sperm</td>
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<tr>
<td>89335</td>
<td>Cryopreservation; reproductive tissue, testicular</td>
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</tr>
<tr>
<td>89337</td>
<td>Cryopreservation; mature oocytes</td>
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<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
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<td>Please refer to ICD-10 Neoplasm table for a complete list of codes.</td>
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<table>
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<tr>
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<tbody>
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</tbody>
</table>

Appendix A

Worldwide cryonics support groups:

- **Australia**: The Cryonics Association of Australasia offers support for Australians or residents of other nearby countries seeking information about cryonics. caalist@prix.pricom.com.au.
Their public relations officer is Philip Rhoades. phil@pricom.com.au. GPO Box 3411 NSW 2001 Australia. Phone: +61 2 8001 6204 (office) or +61 2 9922 6979 (home).

- **Belgium**: A new website in Dutch and French is being set up for Belgian cryonicists. http://users.skynet.be/cryonicsbelgium/. Contact David Verbeke at david.verbeke@scarlet.be or cryonicsbelg@hotmail.com for further information.

- **Canada**: This is a very active group that recently participated in Toronto's first cryopreservation. President, Christine Gaspar, Vice President, Gary Tripp. Visit them at: http://www.cryocdn.org/. There is a subgroup called the Toronto Local Group. Meeting dates and other conversations are held via the Yahoo group. This is a closed group. To join write: csc3@cryocdn.org.

- **Denmark**: A Danish support group is online. Contact them at: david.stodolsky@socialinformatics.org.

- **Finland**: The Finnish Cryonics Society, (KRYOFIN) is a new organization that will be working closely with KrioRus. They would like to hear from fellow cryonicists. Contact them here. Their President is Antti Peltonen.

- **France**: Roland Missionnier has formed SOCIETE CRYONICS de FRANCE He would like to hear from cryonicists in Switzerland, Luxembourg and Monte Carlo. CELL: (0033) 6 64 90 98 41, FAX: (0033) 4 77 46 96 12 or rolandmissionnier@yahoo.fr.

- **Germany**: There are a number of cryonicists in Germany. Their homepage is: www.biostase.de.

- (English version in preparation.) If there are further questions, contact Prof. Klaus Sames sames@uke.uni-hamburg.de.

- **Greece**: Greek Cryonics Support Group. Sotiris Dedeloudis is the Administrator. Find them at: http://www.cryonics.gr/.

- **Ireland**: Cryonics Ireland is a new subgroup of Cryonics UK and is for people in Ireland who are signed up, in the process of signing up, or just interested in Cryonics. They have an Irish-specific website: www.cryonics.ie. Mark Walker can be contacted at: mark@cryonics.ie.

- **Italy**: Giovanni Ranzo and Aldo Fusciardi are located in the Rome area. Giovanni.r@operamail.com. The Italian Cryonics Association (Associazione Italiana Cryonica – AIC), The Life Extension Research Group (Gruppo di per l’Estension della Vita — GREV). www.i-lifegroup.org. The founder is Bruno Lenzi; contact him at: mr.brown88@hotmail or 348.83.97.613.

- **Japan**: Hikaru Midorikawa, is President of the Japan Cryonics Association, formed in 1998. Their goals are to disseminate cryonics information in Japan, to provide cryonics services in Japan and, eventually, to allow cryonics to take root in Japanese society. mid_hikaru@yahoo.co.jp or http://www.cryonics.jp/index-e.html.

- **New Zealand**: Contact Cam Christie, easternhk@hotmail.com, or go to: http://www.nzcryonicssociety.org.nz/.

- **Netherlands**: The Dutch Cryonics Organization is the local standby group and welcomes new enthusiasts (http://www.cryonisme.nl). Contact Secretary Jappie Hoekstra at +31-(0)6-53213893 or email: jh@hoekstra-media.nl.
• **Portugal**: Nuno & Diogo Martins with Rui Freitas have formed a group to aid Alcor members in Portugal. Contact: n-martins@n-martins.com, www.cryonics.com.pt/.

• **Russia**: KrioRus is a new Russian cryonics organization operating in Russia, CIS and Eastern Europe that exists to help arrange cryopreservation and long-term suspension locally, or with CI or Alcor. Please contact krirus@mail.ru or danila.medvedev@mail.ru for additional information, or visit . Phone: 7-905-768-04-57 or +7 (495) 489-52-60.

• **Spain**: Giulio Prisco is Secretary of the Spanish Cryonics Society. http://www.crionica.org.sec. He lives in Madrid and he’s a life member of CI. He is willing to serve as a contact point for Europeans. He can be contacted at (34)610 536144 or giulio@gmail.com.

• **United Kingdom**: The UK has largest number of cryonicists outside the United States. www.cryonics-europe.org is an informative site run by former CI Director John de Rivaz (John@deRivaz.com). Also, a joint CI & Alcor support group known as “Cryonics UK” or “CUK” can be investigated at www.cryonics.uk.com. Secretary, Mark. For signup help, contact David Flude, david.flude114@googlemail.com.

• **International**: The Cryonics Society is a global cryonics advocacy organization. www.CryonicsSociety.org/. Contact by phone at 585-473-3321.